

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

INNOPHARMA LICENSING, INC., INNOPHARMA LICENSING LLC,
INNOPHARMA INC., INNOPHARMA LLC,
MYLAN PHARMACEUTICALS INC., and MYLAN INC.
Petitioner,

v.

SENJU PHARMACEUTICAL CO., LTD., BAUSCH & LOMB, INC., and
BAUSCH & LOMB PHARMA HOLDINGS CORP.
Patent Owner.

U.S. Patent No. 8,871,813 to Sawa *et al*
Issue Date: October 28, 2014

Title: Aqueous Liquid Preparation Containing 2-Amino-3-(4-
Bromobenzoyl)Phenylacetic Acid

Inter Partes Review No: IPR2016-00090

DECLARATION OF PAUL A. LASKAR, PH.D.

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I. Introduction

1. I am over the age of eighteen (18) and otherwise competent to make this declaration.

2. I have been retained as an expert witness on behalf of Petitioner for the above-captioned *inter partes* review (“IPR”). I am being compensated for my time in connection with this IPR at my standard consulting rate, which is \$250 per hour. My compensation is in no way dependent on the outcome of this IPR.

3. I understand that the petition for *inter partes* review involves U.S. Patent No. 8,871,813 (“the ’813 patent”) (EX1001), which was issued on October 28, 2014, from U.S. Application No. 14/261,720 (“the ’720 application”), naming Shirou Sawa and Shuhei Fujita as the inventors. The ’720 application is a division of application No. 14/165,976 (“the ’976 application”), now U.S. Patent No. 8,754,131, which is a division of application No. 13/687,242 application (“the ’242 application”), now U.S. Patent No. 8,669,290, which is a division of application No. 13/353,653 (“the ’653 application”), now U.S. Pat. No. 8,497,304, which is a division of application No. 10/525,006 (“the ’006 application”), which was the U.S. National Stage of PCT Application No. PCT/JP2004/000350 (“the ’350 application”), filed on January 16, 2004, now U.S. Patent No. 8,129,431. The ’350 application claims priority to Japanese Application No. 2003-12427, filed on January 21, 2003. It is my understanding that the earliest possible priority date of

the '813 patent is January 21, 2003, the filing date of the Japanese priority application. I further understand that, according to the USPTO records, the '813 patent is currently assigned to Senju Pharmaceutical Co., Ltd. ("Senju," "the patentee," or "the patent owner").

4. Claim 1 of the '813 patent is reproduced below:

1. A stable aqueous liquid preparation consisting essentially of: (a) a first component; (b) a second component; wherein the first component is 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof; (c) boric acid; (d) sodium tetraborate; and (e) water; wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate; the first component is the sole pharmaceutical active ingredient contained in the preparation and is present in the preparation at a concentration from about 0.05 w/v % to about 0.2 w/v %; the second component is tyloxapol and is present in said liquid preparation in an amount sufficient to stabilize said first component; and wherein said stable liquid preparation is formulated for ophthalmic administration.

(EX1001, 11:30-42).

5. Claims 2-6, 24, and 27 depend directly from Claim 1. Claims 2, 4-6, and 27 recite the concentrations of tyloxapol and/or bromfenac or its sodium salt, the pH of the preparations, and additional additives. Claim 3 recites that the bromfenac is a sodium salt. Claim 24 recites that the preparation does not include any preservative.

6. Claim 7 is reproduced below:

7. A stable aqueous liquid preparation consisting essentially of: (a) a first component; (b) a second component; wherein the first component is 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof; (c) boric acid; (d) sodium tetraborate; and (e) water; wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate; the first component is the sole pharmaceutical active ingredient contained in the preparation and is present in the preparation at a concentration from about 0.05 w/v % to about 0.2 w/v %; the second component is tyloxapol; wherein said stable liquid preparation is formulated for ophthalmic administration; and wherein the stable aqueous liquid preparation is characterized in that greater than about 90% of the original amount of the first component remains in the preparation after storage at about 60° C. for 4 weeks.

(EX1001, 11:64-12:12).

7. Claims 8-12 and 25 depend directly or indirectly from claim 7. Claims 8 and 10-12 recite the concentrations of tyloxapol and/or bromfenac or its sodium salt, the pH of the preparations, and/or additional additives. Claim 9 recites an aqueous formulation of claim 7 in which greater than about 92% of the original amount of bromfenac remains in the preparation after storage at about 60° C for 4 weeks. Claim 25 recites that the preparation does not include any preservative.

8. Claim 13 is reproduced below:

13. A stable aqueous liquid preparation consisting essentially of: (a) a first component; and (b) a second component; wherein the first component is 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof; (c) boric acid; (d) sodium tetraborate; and (e) water; wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate; the first component is the sole pharmaceutical active ingredient contained in the preparation and is present in the preparation at a concentration from about 0.05 w/v % to about 0.2 w/v %; the second component is tyloxapol; wherein said stable liquid preparation is formulated for ophthalmic administration; provided that the liquid preparation does not include mannitol.

(EX1001, 12:39-50).

9. Claims 14-23 and 26 depend directly or indirectly from claim 13. Claims 14, 16-18, 21-23, and 26 recite the concentrations of tyloxapol and/or bromfenac or its sodium salt, the pH of the preparations, and additional additives. Claim 15 recites that the bromfenac is a sodium salt. Claims 19-20 recite a preparation wherein greater than about 90% and 92%, respectively, of bromfenac remains in the preparation after storage at about 60° C for 4 weeks. Claim 26 recites that the preparation does not include any preservative.

10. In preparing this Declaration, in addition to those materials listed above, I have reviewed the '813 patent and considered the file history of the '813

patent, and each of the documents cited herein, in light of general knowledge in the art as of before January 21, 2003. In formulating my opinions, I have relied upon my experience in the relevant art. I have also considered the viewpoint of a person of ordinary skill in the art (“POSA”) (*i.e.*, a person of ordinary skill in the field of ophthalmic formulations and drug delivery including formulation of aqueous liquid anti-inflammatory preparations) as of before January 21 2003. As described in detail below, I offer the following opinions in this declaration:

- a. A POSA would have had reason to combine the disclosures of U.S. Patent. No. 4,910,225 (“Ogawa”) (EX1004) and U.S. Patent No. 6,107,343 (“Sallmann”) (EX1009) to arrive at the claimed invention as recited in independent claims 1, 7, and 13 of the ’813 patent and such a POSA would have had a reasonable expectation of success in making the claimed preparations.
- b. A POSA would have been further motivated to combine Ogawa and Sallmann in view of Australian Patent No. AU-B-22042/88 (“Fu”) (EX1011) to arrive at the claimed invention as recited in independent claims 1, 7, and 13 of the ’813 patent and such a POSA would have had a reasonable expectation of success in making the claimed preparations.
- c. A POSA would have been further motivated to combine Ogawa and Sallmann in view of U.S. Patent No. 6,274,609 (“Yasueda”) (EX1012) to

arrive at the claimed invention as recited in independent claims 1, 7, and 13 of the '813 patent and such a POSA would have had a reasonable expectation of success in making the claimed preparations.

d. The additional features recited in dependent claims 2-6, 8-12, and 14-27 would have been obvious to a POSA in view of Ogawa (EX1004) and Sallmann (EX1009), or in the alternative, in further view of Fu (EX1011), or in further view of Yasueda (EX1012), and when considered in light of the other prior art references discussed in this declaration, which make up the general knowledge in the art related to aqueous formulations of anti-inflammatory drugs for ophthalmic administration. For the reasons discussed in this declaration, a POSA would have had reason to combine the teachings of Ogawa (EX1004) and Sallmann (EX1009), or in the alternative in further view in Fu (EX1011) or Yasueda (EX1012), and when considered in light of the other prior art references discussed in this declaration, to arrive at the claimed inventions of claims 2-6, 8-12, and 14-27 and such a POSA would have had a reasonable expectation of success in making the claimed inventions.

e. I have also considered arguments that may be asserted by Senju regarding objective indicia of nonobviousness. Even in view of these potential arguments, the prior art references discussed in this declaration

would have rendered obvious the claimed invention to a person of ordinary skill in the art.

II. List of documents I considered in formulating my opinion

11. In formulating my opinion, I have considered all documents cited in this Declaration and all documents cited in the Petition for *Inter Partes* Review of U.S. Patent No. 8,871,813, as well as the following documents:

<i>InnoPharma Exhibit #</i>	<i>Description</i>
1001	Sawa <i>et al.</i> , U.S. Patent No. 8,871,813, "Aqueous Liquid Preparation Containing 2-Amino-3-(4-Bromobenzoyl) Phenylacetic Acid"
1002	Certified English translation of: Hara, Yoshiyuki, "Bromfenac sodium hydrate," <i>Clinics & Drug Therapy</i> 19:1014-1015 (2002)
1003	Declaration of Paul A. Laskar, Ph.D.
1004	Ogawa <i>et al.</i> , U.S. Patent No. 4,910,225, "Locally Administrable Therapeutic Composition for Inflammatory Disease"
1005	Desai <i>et al.</i> , U.S. Patent No. 5,603,929, "Preserved Ophthalmic Drug Compositions Containing Polymeric Quaternary Ammonium Compounds"
1006	Desai <i>et al.</i> , U.S. Patent No. 5,558,876, "Topical Ophthalmic Acidic Drug Formulations"
1007	Certified English translation of "Bromfenac sodium hydrate" in the <i>Japanese Pharmacopoeia 2001 Edition</i> : 27-29, Yakuji Nippo Limited (2001)
1008	FDA approved "BROMDAY™ (bromfenac ophthalmic solution, .09%) Product Label," U.S. Approval: March 24, 2005, ISTA Pharmaceuticals, Inc.
1009	Sallmann <i>et al.</i> , U.S. Patent No. 6,107,343, "Ophthalmic And Aural Compositions Containing Diclofenac Potassium"

InnoPharma Exhibit #	Description
1010	Guttman <i>et al.</i> , "Solubilization of Anti-inflammatory steroids by Aqueous Solutions of Triton-WR-1339," <i>Journal of Pharmaceutical Sciences</i> 50: 305-307 (1961)
1011	Fu <i>et al.</i> , Australian Patent No. AU-B-22042/88, "Preservative System For Ophthalmic Formulations"
1012	Yasueda <i>et al.</i> , U.S. Patent No. 6,274,609, "Aqueous Liquid Pharmaceutical Composition Containing as Main Component Benzopyran Derivative"
1013	U.S. Patent Application No. 13/687,242, Office Action of August 1, 2013
1014	U.S. Patent Application No. 10/525,006, Applicant Remarks in support of amendment March 26, 2008
1015	U.S. Patent Application No. 10/525,006, Applicant Remarks in support of amendment, September 6, 2011
1016	<i>The Pharmacopeia of the United States of America</i> , Twenty-Sixth Revision and the National Formulary, Twenty-First Edition
1017	Kapin, <i>et. al.</i> , International Patent No. WO 2002/13804, "Method for Treating Angiogenesis-Related Disorders Using Benzoyl Phenylacetic Acid"
1018	Flach, Allan, "Topical Nonsteroidal Antiinflammatory Drugs for Ophthalmic Uses," <i>Ophthalmic NSAIDs</i> : 77-83 (1996)
1019	Schott, H., "Comparing the Surface Chemical Properties and the Effect of Salts on the Cloud Point of a Conventional Nonionic Surfactant, Octoxynol 9 (Triton X-100), and of Its Oligomer, Tyloxapol (Triton WR-1339)," <i>Journal of Colloid and Interface Science</i> 205: 496-502 (1998)
1020	Regev, O., <i>et al.</i> , "Aggregation Behavior of Tyloxapol, a Nonionic Surfactant Oligomer, in Aqueous Solution," <i>Journal of Colloid and Interface Science</i> 210: 8-17 (1999)
1021	Aviv, H., International Patent No. WO 94/05298, "Submicron Emulsions as Ocular Drug Delivery Vehicles"
1022	Bergamini <i>et al.</i> , U.S. Patent No. 5,597,560, "Diclofenac And Tobramycin Formulations For Ophthalmic And Otis Topical Use"

InnoPharma Exhibit #	Description
1023	U.S. Patent Application No. 13/687,242, Applicant Remarks in support of amendment, November 28, 2012
1024	Excerpt of Plaintiffs' Opening Markman Brief filed in <i>Senju Pharma. Co., Ltd. et al. v. InnoPharma Licensing, Inc. et al.</i> , C.A. No. 1:15-cv-03240-JBA-KMW (D.N.J.) D.I. 16 (Aug. 10, 2015).
1025	U.S. Patent Application No. 13/687,242, Applicant Remarks in support of amendment, October 22, 2013
1026	"monohydrate," Webster's New World Dictionary of the American Language: 920, New World Dictionaries / Simon and Schuster (1980).
1027	"Voltaren," Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, Appl. No. N020037, U.S. FDA, accessed at http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?A_ppl_No=020037&TABLE1=OB_Rx
1028	Yanni <i>et al.</i> , U.S. Patent No. 5,475,034, "Topically Administrable Compositions Containing 3-Benzoylphenylacetic Acid Derivatives for Treatment of Ophthalmic Inflammatory Disorders".
1029	"ISTA Pharmaceuticals Submits New Drug Application for Xibrom™ QD (once-daily)," News Release, ISTA Pharmaceuticals (December 20, 2007)
1030	Prince, S., <i>et al.</i> , "Analysis of benzalkonium chloride and its homologs: HPLC versus HPCE," <i>Journal of Pharmaceutical and Biomedical Analysis</i> 19: 877-882, Elsevier Science B.V., Netherlands (1999)
1031	"Acular®" and "Azopt™," Physician's Desk Reference 54: 486- 487, 491-492 (2000).
1032	Doughty, M., "Medicines Update for optical practitioners- Part 11," <i>Optician</i> 5853 (223), (2002).
1033	Reddy, Indra K., <i>Ocular Therapeutics and Drug Delivery: A Multi-Disciplinary Approach</i> : 42-43, 390 (1996).

<i>InnoPharma Exhibit #</i>	<i>Description</i>
1034	Fan, T., "Determination of Benzalkonium Chloride in Ophthalmic Solutions Containing Tyloxapol by Solid-Phase Extraction and Reversed-Phase High-Performance Liquid Chromatography," Journal of Pharmaceutical Sciences 82 (11): 1172-1174, American Pharmaceutical Association, United States (1993).
1035	Wong, Michelle, International Patent No. WO 94/15597, "Ophthalmic Compositions Comprising Benzyl lauryldimethylammonium Chloride" (filed January 11, 1993; issued July 21, 1994).
1036	Guy <i>et al.</i> , U.S. Patent No. 5,540,930, "Suspension of Loteprednol Etabonate for Ear, Eye, or Nose Treatment" (filed October 25, 1993; issued July 30, 1996).
1037	FDA approved "ALREXTM (loteprednol etabonate ophthalmic suspension) 0.2% Product Label," U.S. Approval: 1998, Bausch & Lomb Pharmaceuticals.
1038	FDA approved "LOTEMAXTM (loteprednol etabonate ophthalmic suspension) 0.5% Product Label," U.S. Approval: 1998, Bausch & Lomb Pharmaceuticals.
1039	"TOBRADEX®" Physician's Desk Reference 54: 490 (2000).
1040	"Alomide® 0.1%" Physician's Desk Reference 50: 469 (1996).
1041	Johnson, R., <i>et al.</i> , U.S. Patent No. 2,880,130, "Anti-Inflammatory Steroid Solutions".
1042	Johnson, R., <i>et al.</i> , U.S. Patent No. 2,880,138, "Anti-Inflammatory Steroid Solutions".
1043	Kawabata <i>et al.</i> , Canadian Patent No. CA 2 383 971 A1, "Prophylactic and Therapeutic Medicaments for Ophthalmic Uses".
1044	Patani, G., <i>et al.</i> , "Bioisoterism: A Rational Approach in Drug Design," Chem. Rev. 96: 3147-3176 (1996).
1045	FDA approved "XIBROMTM (bromfenac ophthalmic solution, .09%) Product Label," ISTA Pharmaceuticals, Inc.

<i>InnoPharma Exhibit #</i>	<i>Description</i>
1046	Senju Pharmaceutical Co., Ltd. Press Releases, "The approval of BRONUCK® (bromfenac sodium hydrate ophthalmic solution) as an import drug in China," http://www.senju.co.jp/ , accessed at http://www.senju.co.jp/english/news/_icsFiles/afieldfile/2009/11/18/2009111814br.pdf , published November 17, 2009, 1 page.
1047	FDA approved "PROLENSATM (bromfenac ophthalmic solution, 0.07%) Product Label," U.S. Approval: April 5, 2013, Bausch & Lomb Incorporated
1048	"Borax (Sodium tetraborate)," Biochemicals and Reagents: 175, Sigma-Aldrich (2000-2001).
1049	Ali, et al., U.S. Patent No. 6,071,904, "Process for Manufacturing Ophthalmic Suspensions".
1050	Story, M., et al., European Patent No. 0274870, "Micelles containing a non-steroidal antiinflammatory compound" (filed December 12, 1987; issued July 7, 1988)
1051	"DuractTM," Physician's Desk Reference 52:3035-3037 (1998).
1052	Curriculum Vitae of Paul A. Laskar, Ph.D.
1053	U.S. Patent Application No. 10/525,006, Applicant Remarks in support of amendment Oct. 25, 2010

III. My background and qualifications

12. I am an expert in the field of formulations and drug delivery, specifically pharmaceutical formulations for ophthalmic administration, including topical aqueous liquid preparations, and I have been an expert in this field since prior to 2003. Throughout the remainder of this declaration, I will refer to the field of ophthalmic formulations, and specifically pharmaceutical formulations

for topical ophthalmic administration, including those comprising anti-inflammatory drugs such as NSAIDs, as the relevant field or the relevant art. In formulating my opinions, I have relied upon my training, knowledge, and experience in the relevant art. A copy of my current curriculum vitae is provided as Exhibit 1052, and it provides a comprehensive description of my academic and employment history.

13. As an expert in the relevant field since prior to 2003, I am qualified to provide an opinion as to what a POSA would have understood, known, or concluded as of 2003. Since 1965, I have accumulated significant training and experience in the relevant field and related fields.

14. I have a Ph.D. in Pharmaceutical Sciences from Oregon State University with a Minor in Biostatistics; a M.B.A. in General Management, International Management and Marketing from the University of California at Irvine; a M.S. in Pharmacy and a B.S. in Pharmacy from the University of Illinois; and a B.A. in General Science (Chemistry, Biology) from the University of Rochester.

15. I am currently, and have been since October 2006, the President of Paul Laskar Associates, Inc., a pharmaceutical development consulting firm which I founded. My client base consists of start-up and established pharmaceutical companies with whom I consult in the areas of pharmaceutical

development, including formulation development and evaluation. A significant fraction of my clients focus on ophthalmic products. From 2003 to 2006, I was Senior Director, Pharmaceutical Development at Dey LP, at that time owned by Merck KGaA. In that capacity I supervised the formulation development, clinical supply, technology transfer, pilot operations, and preclinical functions. While most of Dey's projects were for inhalation, I worked on two generic ophthalmic projects.

16. From 1994 to 2003, I was initially Director, then Vice President, Pharmaceutical Development, and subsequently Principal Director, Pharmaceutics and Technology, at Santen Inc., the U.S. subsidiary of the Japanese ophthalmic pharmaceutical company, Santen Ltd. My responsibilities included directing ophthalmic formulation development, stability assessment, preparation of internal reports and regulatory documents, and review of in-license candidates. The areas I supervised included formulation development, analytical chemistry and stability assessment, clinical supplies, and non-clinical development. During my tenure with Santen Inc., three ophthalmic projects, Quixin, Betimol, and Alamast, resulted in successful New Drug Applications ("NDAs") by the Food and Drug Administration ("FDA") and commercial launch. A fourth NDA, Iquix, and a prostaglandin compound, tafluprost (now marketed in the U.S. as Zioptan®), to which I contributed to its formulation as

well as chemistry, manufacturing and control (“CMC”) development strategy, were approved subsequent to my leaving Santen. Alamast, whose active ingredient is pemirolast potassium, is an acidic drug though not a NSAID (see paragraph 29 for further discussion of acidic drugs). We faced an analogous dilemma regarding turbidity and precipitate formation of pemirolast with BAC. In this case, we were able to solve the issue by choosing the C12-BAC homologue as the quaternary ammonium preservative.

17. From 1993 to 1994, I was Director, Pharmaceutical Development, at CoCensys, a start-up pharmaceutical company. During this time, I directed CMC development of two new chemical entities (“NCE”), one for oral use as a suspension and solid drug product, and the second as a parenteral. The oral NCE was successfully formulated as a suspension and submitted as an investigational new drug (“IND”) application to the FDA.

18. From 1982 to 1993, I was employed by Allergan, Inc., an ophthalmic specialty company. Initially, I was a Scientist, Product Development, then I became a Section Manager and eventually Manager in the same area, and, finally, Director, Product Development. While at Allergan, I was involved in the formulation and subsequent development of a number of ophthalmic and dermatological drug products, many of which were approved as NDAs by the FDA and their equivalents in other countries/jurisdictions. From 1973 to 1982, I

was Assistant Professor of Pharmacy at the College of Pharmacy, University of Illinois-Medical Center (now University of Illinois-Chicago Campuses) and then Associate Professor of Pharmacy at the School of Pharmacy at Creighton University. During this time, among the courses I taught were those in dosage form development including oral solids, ophthalmics, and dermatologicals.

19. At present, I provide consulting services to start-up and established pharmaceutical companies for pharmaceutical projects. The nature of the projects include ophthalmics, sterile parenterals, dermatologicals, and liquid and solid oral drug products. The areas in which I consult include active pharmaceutical ingredient (API) synthesis and qualification, formulation development, stability assessment, analytical development, manufacturing process development and transfer, contract laboratory and manufacturer identification and their management, and preparation of regulatory documents.¹

IV. Person of ordinary skill in the art (POSA)

20. I understand that a POSA is a hypothetical person who is presumed to be aware of all pertinent art, thinks along conventional wisdom in the art, and is a person of ordinary creativity. With respect to the '813 patent, a POSA would

¹ I reserve the right to further explain my background and qualifications in deposition where needed.

have had education and/or experience in ophthalmic formulations and drug delivery, and knowledge of the scientific literature concerning the same, specifically pharmaceutical formulations comprising anti-inflammatory compounds such as NSAIDs, for ophthalmic administration as of 2003. The education and experience levels may vary between persons of ordinary skill, with some persons holding a basic Bachelor's degree, but with 5-10 years of relevant work experience, or others holding more advanced degrees—*e.g.*, Pharm.D., Ph.D., or M.D.—but having fewer years of experience. A POSA may also work as part of a multi-disciplinary 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.

V. The '813 patent

21. I have considered the disclosure of the '813 patent in light of general knowledge in the relevant field as of the earliest possible priority date of the '813 patent, which I understand to be January 21, 2003.

22. The '813 patent specification is directed to an aqueous liquid preparation containing 2-amino-3-(4-bromobenzoyl) phenylacetic acid (otherwise known as its generic name, *bromfenac*), (EX1051, 2-3) or its pharmacologically acceptable salt thereof or a hydrate thereof. (EX1001, 1:8-11). The bromfenac aqueous liquid preparations described in the '813 patent also include an alkyl aryl

polyether alcohol type surfactant or a polyethylene glycol fatty acid ester surfactant. (EX1001, 1:14-16).

23. The '813 patent further specifies that the pharmacologically acceptable salt of bromfenac can be the sodium salt, and that the bromfenac sodium salt can be one of several hydrates: 1/2 hydrate, 1 hydrate or 3/2 hydrate.² (EX1001, 4:2-5). In addition, the '813 patent specifies that among alkyl aryl polyether alcohol type surfactants, tyloxapol is especially preferred. (EX1001, 4:37-39).

24. The '813 patent is more specifically directed to an aqueous liquid ophthalmic preparation containing *bromfenac* and *tyloxapol*, with or without a preservative, such as *benzalkonium chloride* ("BAK," "BAC," or "BKC"), that is stable within a pH range that gives no irritation to the eye, and in which a decrease in the preservative effect of BAC (when present) is inhibited. (EX1001, 2:6-13, 17-23, 49-50).

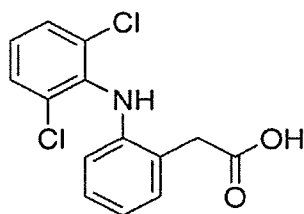
² 1/2 hydrate or hemihydrate corresponds to a ratio of 1 molecule of water per 2 molecules of a drug; 1 hydrate or monohydrate corresponds to a ratio of 1 molecule of water per 1 molecule of a drug; and 3/2 hydrate or sesquihydrate corresponds to a ratio of 3 molecules of water per 2 molecules of a drug. (EX1026, 3).

VI. State of the art as of January 2003

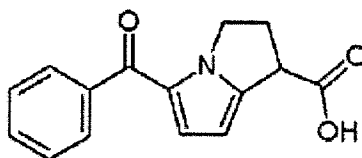
A. Non-steroidal anti-inflammatory compounds were known and approved for ophthalmic use

25. Prior to 2003, non-steroidal anti-inflammatory drugs (NSAIDs) were widely used for managing postoperative ocular inflammation, preventing and treating cystoid macular edema after cataract surgery, preventing intraoperative miosis during cataract surgery, relieving symptoms of seasonal allergic conjunctivitis, and reducing ocular discomfort following refractive surgery. (EX1018, 1:1).

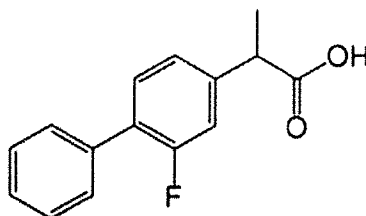
26. As of January 21, 2003, a number of NSAIDs, formulated for ophthalmic use, were FDA-approved and sold in the United States. For example, diclofenac 0.1% (Voltaren® Ophthalmic Solution, Novartis) was approved in 1991 for minimizing postoperative inflammation after cataract surgery. (EX1027). Diclofenac free acid has the following chemical structure:



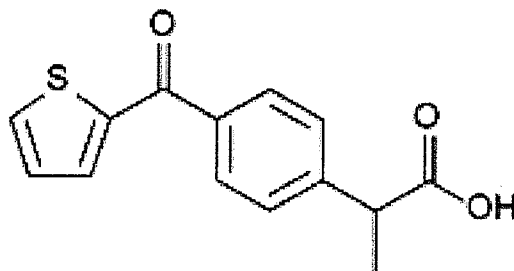
27. An ophthalmic formulation of ketorolac tromethamine 0.5% (Acular® Ophthalmic Solution, Allergan) was approved in 1992 for treating seasonal allergic conjunctivitis. (EX1018, 2:1). Ketorolac free acid has the following chemical structure:



28. Flurbiprofen sodium 0.03% (Ocufen® Ophthalmic Solution, Allergan) and suprofen 1% (Profenal® Ophthalmic Solution from Alcon) were approved in 1986 and 1988, respectively, for inhibiting miosis during cataract surgery. (EX1018, 2:1). Flurbiprofen free acid has the following chemical structure:

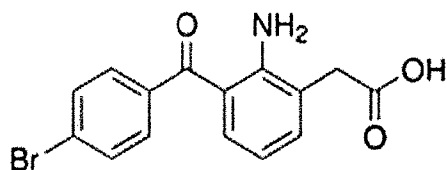


Suprofen free acid has the following chemical structure:



29. The NSAID bromfenac and its salts and hydrates were also known prior to January 21, 2003. (EX1002). Bromfenac, whose structure is shown again below, shares certain structural characteristics with the other NSAIDs, diclofenac,

ketorolac, and flurbiprofen. Specifically, each of these NSAIDs possesses a –CH–COOH group attached to an aryl ring. The–COOH moiety is called a carboxylic acid, and in this report I sometimes refer to these NSAIDs that contain a carboxylic acid moiety as “acidic” NSAIDs. This derives from the fact that at the pH of the ophthalmic solution a substantial fraction of the NSAID is ionized forming a hydrogen ion, H⁺, and an anion corresponding to the remainder of the NSAID molecule. At the pH of the drug product the NSAID anion can then interact with the BAC cation. In most cases, this results in a turbid or hazy drug product and diminishes the antimicrobial preservative effectiveness of the BAC.



30. In fact, by 2003, bromfenac had already been shown to have an enhanced anti-inflammatory action when compared to other known NSAIDs. (EX1002, 2:2:4-3:1:3, 3:2:2; EX1028, 15:1-16:34, Table 1). For example, bromfenac was 4-fold more effective than diclofenac in an *in vitro* cyclooxygenase inhibition assay,³ and was able to inhibit cyclooxygenase 11-fold better than

³ Anti-inflammatory activity of the NSAIDs was tested by polarographically monitoring the inhibition in the rate of oxygen consumption in the conversion of

indomethacin, another NSAID. (EX1028, 15:1-16:34, Table 1; EX1002, 2:1:4-2.3).

31. By 2003, researchers in the field had already prepared and patented ophthalmic preparations of bromfenac. For example, in 1990, over a decade prior to the earliest priority date of the '813 patent, Ogawa disclosed and claimed an ophthalmic formulation of bromfenac containing, among other additives, the surfactant polysorbate 80 and BAC. (EX1004, Abstract, 10:5-18). The formulation described in Ogawa was approved and commercially marketed in Japan in 2000 under the name Bronuck®. (EX1029; EX1007, 4). In 1997, Desai described stable aqueous ophthalmic preparations of bromfenac and described that the formulations could also include, among other additives, a polymeric quaternary ammonium compound, Polyquad®, and tyloxapol. (EX1005, 4:11-55, 3:38-39, 2:35-44, claim 8). In 1995, Yanni described ophthalmic formulations of bromfenac by making ester and amide derivatives of bromfenac. (EX1028, 15:1-16:34, Table 1, 16:54-17:9). Thus, bromfenac ophthalmic formulations had been described and developed prior to January 21, 2003.

arachidonic acid to prostaglandin H₂ by prostaglandin H synthase (cyclooxygenase). (EX1028, 13:25-31).

B. BAC was the preservative of choice in ophthalmic formulations

32. An ophthalmic dosage form intended for multi-dose use requires a preservative, an agent that protects the dosage form from microbiological growth, or other means to ensure the absence of microbial proliferation in the drug product. (EX1005, 1:16-17). By the 1950's, both sterility and maintaining microbiological acceptability were required by FDA regulation. Prior to 2003, one of the most common preservatives in ophthalmic formulations was BAC. According to Prince, over 65% of the ophthalmic products prior to 1995 contained BAC as a preservative. (EX1030, 2:1:1). For example, Acular[®], an ophthalmic formulation that contained the NSAID ketorolac was approved by the FDA in 1992 and was formulated with the preservative BAC. (EX1031, 4-5). Azopt[™], an ophthalmic suspension containing brinzolamide, was approved by the FDA in 1998 and was also formulated with BAC. (EX1031, 2-3). At least three different ophthalmic products were marketed in the United Kingdom (Vivicrom Eye Drops, Nyogel[®] Eye Gel, and Lumigan[®]) that used BAC as the preservative prior to 2003. (EX1032, 3:Table 1). Furthermore, many publications described BAC as the most commonly used, or the preservative of choice, for ophthalmic formulations. (EX1033, 5; EX1005, 1:27-28; EX1011, 4:33-36; EX1034, 3:1). Most notably, Ogawa teaches ophthalmic bromfenac formulations containing BAC (EX1004, Abstract, 10:5-18), one of which was commercially marketed as Bronuck[®].

(EX1029, 1:2; EX1007, 4). Therefore, it was not surprising that by January 2003 researchers preferentially used BAC when preparing ophthalmic formulations of NSAIDs.

33. But prior to 2003, NSAIDs were known to form insoluble complexes when combined with quaternary ammonium preservatives, such as BAC, in aqueous liquid preparations. (EX1006, 1:10-24; EX1005, 1:27-34; EX1022, 2:18-24). These complexes caused the solution to become cloudy or turbid, potentially decreasing the pharmaceutical activity of the drug, and reducing the preservative activity of BAC. (EX1035, 4:11-17; EX1011, 5:1-7).

C. It was known that non-ionic surfactants stabilized aqueous preparations containing an NSAID and BAC

34. Polysorbate 80 and tyloxapol are non-ionic surfactants that were well-known before 2003. (EX1036, 4:15-21). In the late 1980's, a group of Japanese investigators succeeded in stabilizing⁴ bromfenac by using polysorbate 80, polyvinylpyrrolidone (PVP), and a sulfite at a pH of 6-9 – a pH range suitable for topical administration to the eye. (EX1004, 3:48-53, 10:5-18).

⁴ Stability is defined as presence of a minimal change in residue rate of bromfenac and absence of red insoluble matter in the preparations after a period of storage at 60° C. (EX1004, 8:19-22).

35. Tyloxapol belongs to a class of non-ionic surfactants known as ethoxylated octylphenols. (EX1019, 1:2:3-2:1:2). In the late 1980's, Fu⁵ indicated that other non-ionic surfactants in the ethoxylated octylphenol class, such as Octoxynol 9 and Octoxynol 40, can stabilize⁶ aqueous liquid ophthalmic NSAID preparations that contained BAC, even in the absence of PVP or a sulfite. (EX1011, 12:1-11, Example 5). Importantly, preservative efficacy in the preparations of Fu was maintained throughout the 2 year shelf-life. (EX1011, Example 5). Therefore, it was known, prior to 2003, that ethoxylated octylphenol surfactants could eliminate instability caused by the interaction of an acidic NSAID with BAC.

D. Tyloxapol is a non-ionic surfactant that was known and widely used in ophthalmic formulations by January 2003

36. By January 2003, tyloxapol⁷ was a known non-ionic surfactant used to stabilize aqueous ophthalmic preparations of NSAIDs and other acidic drugs.

⁵ I understand that the Fu reference has a related US patent (U.S. Patent No. 5,110,493) which contains a similar disclosure.

⁶ Stability is defined as absence of turbidity and lack of precipitate formation in the preparations. (EX1011, 20:9-17, 21:16-22).

⁷ Tyloxapol is also known by the trade name of Triton WR-1339. (EX1010, 4:1:2.)

Structurally, tyloxapol is an oligomeric form of Octoxynol 9 (Triton X-100), which Fu described as an example of a preferred/useful stabilizer of aqueous ophthalmic formulation of NSAIDs and BAC in the 1980's. (EX1019, 1:1:2; EX1020, 8:2:1, 9:Scheme 1; EX1011, 12:1-11).

37. As I will discuss in more detail below, non-ionic ethoxylated octylphenol surfactants, such as Octoxynol 9 of Fu's invention, were described as more effective than polysorbate 80 in stabilizing aqueous liquid ophthalmic preparations of NSAIDs. (EX1011, 12:1-8, Example 5).

38. Tyloxapol was also commonly used in commercial ophthalmic formulations by January 2003. Various ophthalmic products containing tyloxapol were marketed, including Azopt[®] (Brinzolamide) (for treatment of elevated intraocular pressure), Alrex[®] (Loteprednol) (for temporary relief of the signs and symptoms of seasonal allergic conjunctivitis), Lotemax[®] (Loteprednol) (for treatment of steroid responsive inflammatory conditions of the palpebral and bulbar conjunctiva), Tobradex[®] (Tobramycin & Dexamethasone) (for steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated), and Alomide[®] (Lodoxamide) (for treatment of vernal kerato conjunctivitis, vernal conjunctivitis, and vernal keratitis). (EX1031, 2-3; EX1032, 3:Table 1; EX1037; EX1038; EX1039; EX1040).

39. A number of ophthalmic formulations containing tyloxapol were also described in the prior art by January 2003. For example, Sallmann disclosed an ophthalmic formulation containing tyloxapol, BAC, and an NSAID known as diclofenac. (EX1009, 8:1-15, 4:52-62). Guy disclosed a stable ophthalmic solution containing the steroid, loteprednol, and tyloxapol. (EX1036, 3:31-36, 4:15-29). Desai described stable aqueous ophthalmic preparations of bromfenac and included tyloxapol as one surfactant which could be formulated together with bromfenac. (EX1005, Abstract, 2:18-23, 3:30-45, 6:13-16, 6:25-28). Kapin described aqueous liquid ophthalmic preparations of NSAIDs, such as nepafenac and tyloxapol. (EX1017, 6:8-9, 8:13-22, Formulation 3). In fact, the genus of NSAID compounds described in Kapin includes bromfenac. (EX1017, 4:1-23). Guttman reported that tyloxapol stabilized⁸ three different ophthalmic steroid anti-inflammatory drugs in an aqueous solution. (EX1010, 4:2:2-4:2:4, Table 1).

40. Prior to 2003, it also was known that polysorbate 80 and tyloxapol were often interchangeable in ophthalmic preparations. For example, Johnson

⁸ Guttman reported that tyloxapol solubilized three steroid compounds in aqueous preparations. (EX1010, 4:2:2-4:2:4, Table 1). A POSA would have understood this to mean that the preparation were stable because Guttman remarked that the solutions were clear. (EX1010, 3:1, Abstract).

developed two aqueous steroidal anti-inflammatory ophthalmic solutions that were identical to one another except that one contained tyloxapol, and the other contained polysorbate 80. (EX1041, 4:3-72; EX1042, 3:60-4:64.) Senju formulated ophthalmic solutions and suspensions of an acidic anti-inflammatory drug with either tyloxapol or polysorbate 80 as a surfactant, while using BAC as a preservative. (EX1043, 17:1-2, 30:1-37:18). Therefore, it was known by January 2003 that tyloxapol was a widely-used non-ionic surfactant in aqueous liquid preparations comprising anti-inflammatory agents, and was used interchangeably with polysorbate 80.

41. Tyloxapol, as a surfactant and solubilizing agent, was also known to stabilize negatively charged drugs in aqueous preparations better than polysorbate 80. For example, Yasueda compared tyloxapol and polysorbate 80 in their ability to solubilize and stabilize⁹ aqueous ophthalmic solutions containing the acidic

⁹ Solubility or stability was measured as a residual rate (a synonym is “percent of initial”) of pranlukast in an aqueous solution as well as insoluble deposits, *i.e.*, precipitates. Although no insoluble deposit was observed in any of the tested solutions, there was a larger decrease in the residual rate of pranlukast formulated with polysorbate 80 compared to tyloxapol. (EX1012, 6:47-7:43, Tables 4 and 5.)

drug pranlukast.¹⁰ Yasueda described the difficulty of preparing aqueous formulations using pranlukast, due to the “very low water-solubility.” (EX1012, 1:30-35). Yasueda demonstrated that tyloxapol was better than polysorbate 80 at solubilizing and stabilizing pranlukast in an ophthalmic solution. (EX1012, 6:55-7:43, Tables 4 and 5). Specifically, Yasueda demonstrated that the amount of pranlukast in the solution with polysorbate 80 decreased by 15% after two weeks of storage, and only by 0.5%, on average, during the same time period when using tyloxapol. (EX1012, 6:55-7:43, Tables 4 and 5). Therefore, Yasueda

¹⁰ Pranlukast contains a 5-substituted tetrazole moiety that is considered an acidic functionality, and thus would be considered an acidic drug. (EX1044, 22:2:3-23:1:1). Tyloxapol also appears to prevent possible turbidity due to interaction of the anionic pranlukast with the cationic BAC at the pH of the formulation. Formulation A contains BAC at 50 ppm while Formulation B lacks BAC. Yet, neither results in any precipitate. (EX1012, 6:55-7:20, 7:44-45). This result suggests that pranlukast, much like other acidic drugs bromfenac and diclofenac, forms insoluble complexes when combined with quaternary ammonium preservatives, such as BAC, in aqueous liquid preparations. (EX1053, 1 (“[B]romfenac used in the claimed preparation is an acidic ‘NSAID’ drug.”)).

demonstrated that tyloxapol increased the stability of pranlukast by, on average, a factor of 30.¹¹ Yasueda also noted that when using polysorbate 80, additional stabilizers were needed to achieve drug content in solution greater than 95%. (EX1012, 7:37-43).

42. In summary, prior to January 21, 2003, the prior art in the field of drug delivery and formulation of aqueous liquid preparations described various stable aqueous formulations comprising acidic drugs such as NSAIDs, and in particular bromfenac. In these formulations, BAC was the overwhelmingly most common preservative. Non-ionic surfactants were also used to stabilize these formulations because of the known problems associated with formulating bromfenac and BAC. And in particular, tyloxapol was a non-ionic surfactant

¹¹ Yasueda demonstrated that 85.0% of pranlukast remained in solution when using polysorbate 80. (EX1012, Table 5). When using tyloxapol, 99.6% of pranlukast remained in solution. (EX1012, Table 5). Stated otherwise, the amount of pranlukast remaining in the preparation with polysorbate 80 decreased by 15% after two weeks, and only by 0.4-0.6% with tyloxapol. Accordingly, tyloxapol increased the stability of pranlukast by, on average, a factor of 30 ($15/0.5 = 30$) compared with polysorbate 80.

known to be useful in a number of ophthalmic formulations including those of bromfenac and other NSAIDs and acidic drugs.

E. There is nothing inventive in the '813 patent in view of the prior art

43. PROLENSA[®] – the commercial embodiment of some of the claims of the '813 patent – is a slight variation by Senju of its old ophthalmic preparation of bromfenac. In PROLENSA[®] Senju has introduced nominal changes to its previous formulation, marketed as BRONUCK[®], XIBROM[®], and BROMDAY[®].

44. The initial aqueous ophthalmic preparation of 0.1% bromfenac sodium sesquihydrate, described in Ogawa, was marketed in Japan as of 2000 under the trade name of BRONUCK[®]. (EX1001, 1:19-47; EX1007, 4, Table 1; EX1004, 3:16-5:4, 14:65-16:44). The BRONUCK[®] formulation included bromfenac sodium sesquihydrate, boric acid, borax¹², sodium sulfite, sodium EDTA, povidone, polysorbate 80, and BAC, and had a pH of 8.0-8.6. (EX1007, 4:Table 2; EX1004, 3:16-5:4; 14:65-16:44). In the United States, an identical formulation to BRONUCK[®] of 0.09% bromfenac sodium sesquihydrate was approved by the FDA on March 3, 2005, and was sold under the trade name XIBROM[®]. (EX1045; EX1046). On October 16, 2010, the FDA approved BROMDAY[®] – another aqueous liquid ophthalmic preparation of 0.09%

¹² Borax is another name for sodium tetraborate. (EX1048, 3).

bromfenac sodium sesquihydrate, also originally described by Ogawa. (EX1008). The formulation of BROMDAY[®] was identical to that of XIBROM[®], with the only differences being that XIBROM[®] was dosed twice a day at 0.45 mg bromfenac in each dose (equaling 0.9 mg per day), while BROMDAY[®] was dosed once a day at 0.9 mg bromfenac in each dose. (EX1008; EX1045). Three years later, on April 5, 2013, the FDA approved PROLENSA[®]. (EX1047). PROLENSA[®] is an aqueous liquid ophthalmic preparation of 0.07% bromfenac sodium sesquihydrate, formulated with BAC, boric acid, sodium EDTA, povidone, sodium borate, sodium sulfite, and tyloxapol, at pH 7.8. The only difference between the ingredients of XIBROM[®], BROMDAY[®], and PROLENSA[®] is that PROLENSA[®] contains tyloxapol instead of polysorbate 80. (EX1008; EX1045; EX1047). Thus, the formulation for PROLENSA[®] which is encompassed by certain claims of the '813 patent, introduces only nominal changes to the BRONUCK[®], XIBROM[®] and BROMDAY[®] formulations.

VII. Obviousness of Claims 1-27 of the '813 patent

A. The basis of my analysis with respect to obviousness

45. I understand that an obviousness analysis involves comparing a patent claim to the prior art to determine whether the claimed invention would have been obvious to a POSA in view of the prior art, and in light of the general knowledge

in the art. I also understand that when a POSA would have reached the claimed invention through routine experimentation, the invention may be deemed obvious.

46. I understand that obviousness can be established by combining or modifying the teachings of the prior art to achieve the claimed invention. It is also my understanding that where there is a reason to modify or combine the prior art to achieve the claimed invention, there must also be a reasonable expectation of success in so doing. I understand that reasons to combine prior art references can come from a variety of sources, not just the prior art itself or the specific problem the patentee was trying to solve. And I understand that the prior art references themselves need not provide a specific hint or suggestion of the alteration needed to arrive at the claimed invention; the analysis may include recourse to logic, judgment, and common sense available to a POSA.

47. I understand that patent claims may be considered obvious if they recite subject matter that would have been obvious to a POSA to try and develop. I understand that claims are obvious to try when there is market pressure to solve a problem, and when there are only a finite number of identified, predictable solutions to that problem.

48. I understand that when considering the obviousness of an invention, one should also consider whether there are any objective indicia that support the nonobviousness of the invention. I understand that objective indicia of

nonobviousness include failure of others, copying, unexpectedly superior results, perception in the industry, commercial success, and long-felt but unmet need. I also understand that in order for objective indicia of nonobviousness to be applicable, the indicia must have some nexus to the subject matter in the claim that was not known in the prior art. I understand that this nexus includes a factual connection between the subject matter of the claim and the objective indicia alleged.

B. Obviousness Ground 1 – Ogawa and Sallmann

49. A POSA would have had a reason to combine the disclosures of Ogawa and Sallmann to arrive at the claimed inventions with a reasonable expectation of success.

50. I have been informed that U.S. Patent No. 4,910,225 (“Ogawa”) to Takahiro Ogawa *et al.*, titled “Locally Administrable Therapeutic Composition for Inflammatory Disease,” issued on March 20, 1990, qualifies as prior art to the challenged claims of the ’813 patent. (EX1004). Ogawa describes a specific example (Example 6) of an aqueous preparation comprising the sodium salt of bromfenac (sodium 3-(4-bromobenzoyl)-20aminophenylacetate monohydrate), BAC and the non-ionic surfactant polysorbate 80.

EXAMPLE 6
Ophthalmic Solution

Sodium 3-(4-bromobenzoyl)-2-aminophenyl-acetate monohydrate	0.1 g
Boric acid	1.25 g
Borax	1.0 g
Disodium edetate	0.02 g
Benzalkonium chloride	0.005 g
Polysorbate 80	0.15 g
Polyvinyl pyrrolidone	2.0 g
Sodium sulfite	0.2 g
Sterile purified water	To make 100 ml
pH 8	

(EX1004, 10:5-18).

51. I have been informed that U.S. Patent No. 6,107,343 (“Sallmann”) to Alfred Sallmann *et al.*, titled “Ophthalmic and Aural Compositions Containing Diclofenac Potassium,” issued on August 22, 2000, qualifies as prior art to the challenged claims of the ’813 patent. (EX1009). Sallmann describes a specific example (Example 2) of an aqueous preparation comprising diclofenac potassium, BAC and the non-ionic surfactant tyloxapol.

EXAMPLE 2

Formulation of diclofenac potassium eye drops (0.05%)

diclofenac potassium	0.50 mg/ml
benzalkonium chloride	0.05 mg/ml
disodium edetate	1.0 mg/ml
tyloxapol	1.0 mg/ml
γ -cyclodextrin	20.0 mg/ml
tromethamine	1.0 mg/ml
hydrochloric acid 10%	1.3 mg/ml
sorbitol	46.0 mg/ml
deion. water ad.	1.00 ml

(EX1009, 8:1-15).

1. Claim 1

52. Claim 1 would have been obvious to a POSA reading Ogawa in view of Sallmann as shown below.

'813 patent claim 1	Disclosure in Ogawa (EX1004) and Sallmann (EX1009)
1. A stable aqueous liquid preparation consisting essentially of:	Ogawa Example 6 (EX1004, 10:5-18) and Sallmann Example 2 (EX1009, 8:1-15) are both aqueous liquid preparations. Ogawa Table 11 describes that in Example 6 Ophthalmic Solution, after 4 weeks of 60° C is not less than 90% of the original amount of bromfenac (EX1004, 10:50-57 and 14:45-50).
(a) a first component; (b) a second component;	See below.

'813 patent claim 1	Disclosure in Ogawa (EX1004) and Sallmann (EX1009)
wherein the first component is 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof;	Ogawa Example 6 Ophthalmic Solution contains sodium 3-(4-bromobenzoyl)-2-aminophenylacetate (bromfenac) monohydrate. (EX1004, 10:5-9).
(c) boric acid;	Ogawa Example 6 Ophthalmic Solution contains boric acid. (EX1004, 10:5-18).
(d) sodium tetraborate; and	Ogawa Example 6 Ophthalmic Solution contains sodium tetraborate (borax). (EX1004, 10:5-18).
(e) water;	Ogawa Example 6 Ophthalmic Solution contains sterile purified water. (EX1004, 10:5-18).
wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate;	Ogawa Example 6 Ophthalmic Solution contains sodium 3-(4-bromobenzoyl)-2-aminophenylacetate (bromfenac) monohydrate. (EX1004, 10:5-9).
the first component is the sole pharmaceutical active ingredient contained in the preparation	Ogawa Example 6 Ophthalmic Solution contains sodium 3-(4-bromobenzoyl)-2-aminophenylacetate (bromfenac) monohydrate as the sole pharmaceutical active ingredient
and is present in the preparation at a concentration from about 0.05 w/v % to about 0.2 w/v %;	Ogawa Example 6 Ophthalmic Solution contains 0.1 grams per 100 mL of sodium 3-(4-bromobenzoyl)-2-aminophenylacetate (bromfenac) monohydrate corresponding to a concentration of 0.1 w/v %. (EX1004, 4:42-46)
the second component is tyloxapol	Sallmann Example 2 contains tyloxapol. (EX1009, 8:1-10).

'813 patent claim 1	Disclosure in Ogawa (EX1004) and Sallmann (EX1009)
and is present in said liquid preparation in an amount sufficient to stabilize said first component; and	<p>Sallmann states “[a]nother preferred solubilizer is tyloxapol. The concentration used depends especially on the concentration of the active ingredient. The amount added is typically sufficient to solubilize the active ingredient.” (EX1009, 4:62-65).</p> <p>Sallmann Example 2 contains 1.0 mg/ml of tyloxapol, corresponding to 0.1 w/v % (EX1009, 8:1-10). The amount of tyloxapol disclosed in Sallmann Example 2 is sufficient to stabilize the first component. Compare to '813 patent 5:20-25 (disclosing a tyloxapol minimum content of about 0.01 w/v % and a maximum content of about 0.5 w/v %).</p> <p>Ogawa Table 11 describes that Example 6 Ophthalmic Solution, after 4 weeks at 60° C is not less than 90% of the original amount of bromfenac (EX1004, 10:50-57 and 14:45-50).</p>

'813 patent claim 1	Disclosure in Ogawa (EX1004) and Sallmann (EX1009)
<p>wherein said stable liquid preparation is formulated for ophthalmic administration.</p>	<p>Ogawa: “An ophthalmic composition according to the invention can treat effectively inflammatory eye disease ...” (EX1004, Abstract).</p> <p>“The present invention...provides a therapeutic composition for administration to the eye for the treatment of inflammatory eye diseases...” (EX1004, 2:47-50).</p> <p>“The ophthalmic compositions according to the invention can be prepared in the form of eye drops, eye ointments, and so on...” (EX1004, 3:31-33).</p> <p>Sallmann: “[t]he present invention relates to an ophthalmic composition for treating inflammatory ocular conditions, for treating glaucoma...which composition comprises a therapeutically effective amount of diclofenac potassium and a carrier.” (EX1009, 1:60-65).</p> <p>“The present invention relates also to a method of treating inflammatory ocular conditions, which method comprises administering topically to the eye of a patient requiring such treatment a therapeutically effective amount...” (EX1009, 3:20-24).</p>

2. Claim 7

53. Claim 7 would have been obvious to a POSA reading Ogawa in view of Sallmann, as shown below. Similar to Claim 1, Ogawa’s Example 6 is directed to “[a] stable aqueous liquid preparation” because it is an aqueous ophthalmic solution and Ogawa Table 11 shows that the solution of Example 6, after 4 weeks

of 60° C, is not less than 90% of the original amount of bromfenac. (EX1004, 10:5-18, 10:50-57 and 14:45-50). Sallmann Example 2 is also an aqueous ophthalmic solution. (EX1009, 8:1-15). Ogawa's Example 6 also discloses "2-amino-3-(4-bromobenzoyl) phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof," because it contains sodium 3-(4-bromobenzoyl)-2-aminophenyl-acetate (bromfenac) monohydrate. (EX1004, 10:5-9). Ogawa's Example 6 also discloses boric acid, sodium tetraborate (borax), and water. (EX1004, 10:5-18).

54. Ogawa's Example 6 also discloses that the hydrate form of bromfenac is "at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate," that bromfenac is "the sole pharmaceutical active ingredient . . . and is present in the preparation at a concentration from about 0.05 w/v % to about 0.2 w/v %." Ogawa Example 6 Ophthalmic Solution contains sodium 3-(4-bromobenzoyl)-2-aminophenyl-acetate (bromfenac) *monohydrate* as the sole pharmaceutical active ingredient, wherein the preparation contains 0.1 grams per 100 mL of sodium 3-(4-bromobenzoyl)-2-aminophenyl-acetate (bromfenac) monohydrate, corresponding to a concentration of 0.1 w/v %. (EX1004, 4:42-46 & 10:8-9).

55. Ogawa's Example 6 does not disclose tyloxapol, however, Sallmann Example 2 contains tyloxapol. (EX1009, 8:1-10).

56. Ogawa's Example 6 is also a "stable liquid preparation [that] is formulated for ophthalmic administration and wherein the stable aqueous liquid preparation is characterized in that greater than about 90% of the original amount of the first component remains in the preparation after storage at about 60° C. for 4 weeks." Ogawa is directed to an ophthalmic composition for administration to the eye. (EX1004, Abstract, 2:47-50, 3:31-33). Ogawa Table 11 describes that Example 6 Ophthalmic Solution, after 4 weeks at 60° C is not less than 90% of the original amount of bromfenac (EX1004, 10:50-57 and 14:45-50). Sallmann relates to an ophthalmic composition for treating inflammatory ocular conditions. (EX1009, 1:60-65, 3:20-24). Sallmann also states "[a]nother preferred solubilizer is tyloxapol. The concentration used depends especially on the concentration of the active ingredient. The amount added is typically sufficient to solubilize the active ingredient." (EX1009, 4:62-65). Further, Sallmann Example 2 contains 1.0 mg/ml of tyloxapol, corresponding to 0.1 w/v %. (EX1009, 8:1-10). The amount of tyloxapol disclosed in Sallmann Example 2 is within the general disclosure of the '813 patent, which teaches a tyloxapol minimum content of about 0.01 w/v % and a maximum content of about 0.5 w/v %. (EX1001, 5:20-25).

3. Claim 13

57. Claim 13 would have been obvious to a POSA reading Ogawa in view of Sallmann, as shown below. Similar to Claim 1, Ogawa's Example 6 is directed

to “[a] stable aqueous liquid preparation” because it is an aqueous ophthalmic solution and Ogawa Table 11 shows that the solution of Example 6, after 4 weeks of 60° C, is not less than 90% of the original amount of bromfenac. (EX1004, 10:5-18, 10:50-57 and 14:45-50). Sallmann Example 2 is also an aqueous ophthalmic solution. (EX1009, 8:1-15). Ogawa’s Example 6 also discloses “2-amino-3-(4-bromobenzoyl) phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof,” because it contains sodium 3-(4-bromobenzoyl)-2-aminophenyl-acetate (bromfenac) monohydrate. (EX1004, 10:5-9). Ogawa’s Example 6 also discloses boric acid, sodium tetraborate (borax), and water. (EX1004, 10:5-18).

58. Ogawa’s Example 6 also discloses that the hydrate form of bromfenac is “at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate,” that bromfenac is “the sole pharmaceutical active ingredient . . . and is present in the preparation at a concentration from about 0.05 w/v % to about 0.2 w/v %.” Ogawa Example 6 Ophthalmic Solution contains sodium 3-(4-bromobenzoyl)-2-aminophenyl-acetate (bromfenac) *monohydrate* as the sole pharmaceutical active ingredient, wherein the preparation contains 0.1 grams per 100 mL of sodium 3-(4-bromobenzoyl)-2-aminophenyl-acetate (bromfenac) monohydrate, corresponding to a concentration of 0.1 w/v %. (EX1004, 4:42-46 & 10:8-9).

59. Ogawa's Example 6 does not disclose tyloxapol, however, Sallmann Example 2 contains tyloxapol. (EX1009, 8:1-10).

60. Ogawa's Example 6 is also a "stable liquid preparation [that] is formulated for ophthalmic administration." Ogawa is directed to an ophthalmic composition for administration to the eye. (EX1004, Abstract, 2:47-50, 3:31-33). Sallmann elates to an ophthalmic composition for treating inflammatory ocular conditions. (EX1009, 1:60-65, 3:20-24). Sallmann also states "[a]nother preferred solubilizer is tyloxapol." (EX1009, 4:62). The concentration used depends especially on the concentration of the active ingredient.

61. Neither Ogawa's Example 6 nor Sallmann's Example 2 contains mannitol.

4. Further Discussion Regarding Claims 1, 7, and 13

62. Claims 1, 7, and 13 of the '813 patent are directed to a stable aqueous liquid preparation of bromfenac "consisting essentially of" certain recited ingredients, including bromfenac and tyloxapol. (EX1001, 11:30-12:50). It is my understanding that when a claim contains the phrase "consisting essentially of," it includes the ingredients recited in the claim and is open to additional unrecited ingredients that do not materially affect the basic and novel properties of the claimed subject matter. A POSA would have recognized that the alleged basic and novel properties of the claimed ophthalmic preparations of bromfenac are its

stability and maintenance of its preservative efficacy. This is because the specification of the '813 patent indicates so: “the aqueous solution [described in the '813 patent] becomes stable within a pH range giving no irritation to eyes, and change of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid over time can be inhibited, and . . . when the aqueous solution contains a preservative, deterioration in the preservative effect of said preservative can be inhibited for a long period of time.” (EX1001, 2:29-35, Abstract, 2:6-13).

63. Further, as it appears in the '813 patent, in my opinion, the word “stable” should at least mean “the ability to resist degradation such that the amount of active ingredient remaining in the solution after storage at 60° C for four weeks is not less than 90%.” The specification of the '813 patent provides two examples with respect to the stability of the claimed invention—Experimental Example 1 and 2. (EX1001, 6:34-8:5). The specification states that “the remaining rate of sodium 2-amino-3-(4-bromobenzoyl)phenyl acetate in the compositions . . . is not less than 90% after storage at 60° C. for 4 weeks,” and explains that these results “indicate[] that those compositions have sufficient stability for eye drops.” (EX1001, 7:42-8:5). In other words, I understand the '813 specification to teach that an eye drop wherein less than 90% of the original content of active ingredient remained in the solution after 4 weeks of storage at 60° C would not be stable. Ogawa Table 11 shows that amount of bromfenac remaining after 4 weeks at 60° C

is about 100%, thus is not less than 90% of the original amount and would mean the amount of the surfactant included is sufficient to stabilize the formulation. (EX1004, 10:50-57, 14:45-50). Further, Sallmann also teaches that the amount of surfactant to be added “is typically sufficient to solubilize the active ingredient,” and Example 2 discloses 1.0 mg/ml of tyloxapol, corresponding to 0.1 w/v %, which falls within the general range disclosed by the '813 patent. (EX1009, 4:62-65, 8:1-10). Combined, Ogawa and Sallmann suggested that the formulation resulting from the combination of Ogawa's Example 6 and Sallmann's Example 2 would have had a sufficient amount of tyloxapol to stabilize the bromfenac, and that motivates a POSA to adjust the amount of tyloxapol to an appropriate amount. It is my further opinion that a POSA would have a reasonable expectation of success in formulating a stable aqueous ophthalmic formulation containing bromfenac wherein the amount of bromfenac remaining after storage at 60° C for 4 weeks would be greater than 90%.

64. Ogawa discloses that bromfenac is effective against inflammatory disease of the eye when administered topically. (EX1004, 1:60-68). Ogawa further discloses stable aqueous ophthalmic formulations of bromfenac. (EX1004, 2:10-13). Specifically, Ogawa discloses that the stability of the described formulation of bromfenac is enhanced by incorporating into the formulation polysorbate 80, polyvinylpyrrolidone, and a sulfite, and adjusting the pH to 6.0--

9.0, or preferably, 7.5-8.5. (EX1004, 3:49-53, Experimental Examples 4-5, Example 6, Example 8).

65. Ogawa also provides many examples of the disclosed formulations. (EX1004, Examples 1-9). Ogawa's Example 6, as reproduced above in paragraph 50, is an aqueous liquid ophthalmic preparation of bromfenac sodium monohydrate formulated at a pH of 8 with boric acid, borax, disodium edetate, benzalkonium chloride, polysorbate 80, polyvinylpyrrolidone (PVP), and sodium sulfite. (EX1004, Example 6). Ogawa describes the results of tests of this formulation for stability and concludes that no change in appearance and no decomposition of bromfenac are observed after 4 weeks at 60° C. (EX1004, 10:50-57, 14:46-48, Table 11).

66. A POSA would have understood that in the preparation of Ogawa's Example 6, stability (*i.e.*, the purported basic and novel properties of the preparation of claim 1 of the '813 patent) would not be adversely affected by the inclusion of PVP, BAC, sodium sulfite, and disodium edetate into the aqueous ophthalmic preparations of bromfenac. This is because (1) Ogawa makes no mention of loss in stability for Example 6 and (2) the '813 patent describes and claims that additional ingredients, including sodium edetate, benzalkonium chloride, PVP, and sodium sulfite, may be added to the formulation of claims 1 and 13. (EX1001, 5:39-61). These additional ingredients, which are also found in the

preparations of Ogawa, would be understood by a POSA to not adversely affect the stability of the preparation of Ogawa's Example 6, as Ogawa explains that in preparing the ophthalmic compositions of the claimed invention, a POSA may add additives such as an isotonicizing agent, a microbicidal agent or preservative (*i.e.* benzalkonium chloride, borax, or boric acid), a chelating agent (*i.e.* sodium edetate), and a thickening agent (*i.e.* PVP) "in accordance with the general practice of ophthalmic preparation manufacture." (EX1004, 4:21-26, Example 6).

67. Example 2 in Sallmann describes an ophthalmic formulation containing diclofenac (an acidic NSAID), BAC, and tyloxapol. (EX1009, 8:1-15). The key difference between the ophthalmic formulation of Example 2 in Sallmann and the ophthalmic preparation recited in claims 1, 7, and 13 of the '813 patent is that the acidic NSAID in Sallmann's example is diclofenac potassium, whereas the acidic NSAID in claims 1, 7, and 13 is bromfenac, or a pharmacologically acceptable salt or a hydrate thereof.

68. The other ingredients of Sallmann's Example 2—disodium edetate, γ -cyclodextrin, tromethamine, hydrochloric acid, sorbitol—do not adversely affect the stability or the preservative efficacy of the claimed formulation. This is because, first, Sallmann makes no mention of any adverse impact on stability or preservative efficacy caused by the presence of these additional ingredients. Second, many of these ingredients were included in ophthalmic formulations prior

to 2003. In fact, the '813 patent itself identifies many of these ingredients in a listing of "conventional" additives used in the claimed formulations, and specifically recites them in claims 6, 12, 18 and 24 which depend directly or indirectly from claims 1, 7, and 13. (EX1001, 5:43-61, claims 6, 12, 18, and 24).

69. Claim 7 differs slightly from claim 1 in that it recites the additional limitation that "greater than about 90%" of the original bromfenac remains in the solution after storage for 4 weeks at 60° C. Ogawa's Example 6 is an aqueous liquid ophthalmic preparation of bromfenac sodium monohydrate formulated at the pH of 8. (EX1004, Example 6). Ogawa describes the results of tests of this formulation for stability and concludes that no change in appearance and no decomposition of bromfenac are observed after 4 weeks at 60° C. (EX1004, 10:50-57, 14:46-48, Table 11).

70. Similarly, claim 13 differs from claim 1 in that it requires that the stable aqueous solution does not contain mannitol. Neither Ogawa's Example 6 nor Sallmann's Example 2 contain mannitol. As such, a POSA would have had a reasonable expectation of success formulating a stable ophthalmic aqueous formulation that did not contain mannitol.

71. A POSA would have had reasons to combine Ogawa's disclosure of an aqueous liquid ophthalmic preparation containing diclofenac, and polysorbate 80, with the disclosure of Sallmann to arrive at the aqueous liquid ophthalmic

preparation of claims 1, 7, and 13 of the '813 patent. In my opinion, it would have been obvious to employ the surfactant tyloxapol from Sallmann's Example 2 in place of the surfactant polysorbate 80 in Ogawa's Example 6.

72. First, a POSA would have combined the teachings of Ogawa and Sallmann since both Ogawa and Sallmann relate to ophthalmic formulations of acidic NSAIDs containing BAC and a non-ionic surfactant. Specifically, Ogawa teaches stable ophthalmic formulations containing bromfenac (an acidic NSAID) and polysorbate 80 (a non-ionic surfactant), and Sallmann teaches that tyloxapol (another non-ionic surfactant) was one preferred surfactant for use in aqueous ophthalmic preparations of diclofenac (another acidic NSAID). (EX1004, 10:5-18; EX1009, 4:62). A POSA would have known that substituting tyloxapol for polysorbate 80 would successfully, and predictably, result in a stable ophthalmic formulation of bromfenac because the prior art described stable ophthalmic formulations of acidic NSAIDs, such as bromfenac, containing a non-ionic surfactant, like tyloxapol or polysorbate 80, (EX1004, 3:48-53, 10:5-18; EX1011, 12:1-8; EX1019, 1:1:2; EX1020, 8:2:1, 9:Scheme 1; EX1009, 8:1-15) and tyloxapol and polysorbate 80 had previously been used interchangeably as non-ionic surfactants in ophthalmic formulations. (EX1021, 13:8-10; EX1022, 4:24-31). Further, Ogawa teaches that the aqueous liquid bromfenac preparations

formulated with polysorbate 80 will be useful for ophthalmic administration. (EX1004, 10:5-18).

73. Furthermore, it would have been obvious for a POSA to prepare an aqueous ophthalmic preparation of bromfenac formulated with tyloxapol instead of polysorbate 80 because Sallmann teaches that tyloxapol is a preferred solubilizer for the NSAID, diclofenac, formulation. (EX1009, 4:56-62).

74. A POSA would also have had a reasonable expectation of success that the preparations as claimed would work as ophthalmic preparations. As described above, Ogawa sets forth the excipients for the aqueous preparation of bromfenac and provides an expectation that an aqueous liquid preparation of bromfenac formulated with polysorbate 80 will be useful for ophthalmic administration. (EX1004, 10:5-18). And Sallmann teaches that tyloxapol is a preferred solubilizer for the aqueous ophthalmic preparations of diclofenac. (EX1009, 4:52-62). Therefore, a POSA would have reasonably expected to be able to make and use an aqueous liquid ophthalmic preparation within the scope of claims 1, 7, and 13 of the '813 patent.

75. Other prior art references, which form the basis of the knowledge of a POSA, taught that the use of tyloxapol as a solubilizer can be superior to polysorbate 80 for stabilizing acidic drugs in aqueous preparations containing BAC. Yasueda teaches that tyloxapol can be used as a non-ionic surfactant in an

aqueous liquid ophthalmic formulation to maintain the stability of the acidic drug, pranlukast. (EX1012, 7:34-45). Yasueda further teaches that the use of tyloxapol as a solubilizer and a stabilizer is 30-fold more effective than polysorbate 80 in stabilizing pranlukast in aqueous liquid formulations.¹³ (EX1012, Table 5).

76. Other prior art references, which form the basis of the knowledge of a POSA, taught that bromfenac was superior to diclofenac as an NSAID, and would have further provided motivation for a POSA to combine the formulation in Ogawa's Example 6, which uses bromfenac, with Sallmann's Example 2. For example, Hara describes a new ophthalmic formulation of bromfenac sodium hydrate for the treatment of inflammation of the outer ocular area to post-operative inflammation of the anterior ocular segment and compares it with existing ophthalmic NSAIDs, including diclofenac. (EX1002, 2:1:2). Hara states that bromfenac shows superior efficacy in treating eye inflammation. (EX1002, 3:2:2). Hara discloses that bromfenac "is indicated for use in a broad range of conditions, from inflammation of the outer ocular area to post-operative inflammation of the

¹³ As I discussed previously in footnote 11 of this Declaration, Yasueda demonstrated that the use of tyloxapol as a solubilizer increased the stability of pranlukast relative to polysorbate 80 by, on average, a factor of 30. (EX1012, Table 5).

anterior ocular segment.” (EX1002, 2:1:2). In contrast, Hara states that “the range of application [of diclofenac] is limited.” (EX1002, 2:2:5-3:1:1). The ophthalmic formulation of bromfenac disclosed in Hara is an aqueous liquid preparation of 0.1 w/v % of bromfenac sodium hydrate formulated with benzalkonium chloride, in addition to buffers and stabilizers, at a pH of 8.0 ~ 8.6. (EX1002, 3:1:1).

77. A POSA reading Sallmann and Ogawa would have had further reason to combine their disclosures as claimed because the state of the art, as disclosed in Hara, for example, teaches that bromfenac sodium hydrate is broadly applicable for treatment of various ophthalmic conditions, as compared to diclofenac. A POSA, reading Ogawa and Sallmann, would have known about references such as Hara, and would have been motivated to formulate a preparation that used bromfenac sodium monohydrate as disclosed in Ogawa’s Example 6, and modified it according to Sallmann’s Example 2 formulation to obtain an ophthalmic preparation with superior properties in treating a range of ophthalmic conditions.

78. Furthermore, a POSA would have known that substituting bromfenac for diclofenac would have yielded predictable results because both are NSAIDs with similar physical and pharmacological properties. (EX1002, 2:1:4-2:2:1). Moreover, it would have been obvious for a POSA to combine the teachings of Ogawa with Sallmann to prepare an aqueous ophthalmic preparation with bromfenac because the state of the art, including Hara, for example, teaches that

there were only four NSAID ophthalmic drugs available on the market by 2003, “resulting in limited choices.” (EX1002, 2:2:2).

79. A POSA would also have had a reasonable expectation of success that the preparations as claimed would work as ophthalmic preparations. As described above, Ogawa and Sallmann set forth excipients for an aqueous liquid ophthalmic formulation of an NSAID. Moreover, references such as Hara provide an expectation that an aqueous liquid preparation of bromfenac will be broadly applicable. Therefore, a POSA would have reasonably expected to be able to make and use an aqueous liquid ophthalmic preparation within the scope of claims 1, 7 and 13 of the '813 patent.

80. A POSA would have had a reasonable expectation of success for an aqueous liquid preparation of bromfenac formulated with tyloxapol based on additional prior art references such as Fu. (EX1011). Fu indicates that ethoxylated octylphenol surfactants, such as Octoxynol 9 or Octoxynol 40, can stabilize aqueous liquid preparations of NSAIDs and BAC. (EX1011, 12:1-11, Example 5). A POSA would have known that tyloxapol is an oligomer of Octoxynol 9, and that both are ethoxylated octylphenol surfactants. (EX1019, 1:1:1-2:1:2; EX1020, 8:2:1). In fact, tyloxapol (Triton WR1339) and Octoxynol 9 (Triton X-100) have been used interchangeably in manufacturing ophthalmic preparations. (EX1049, 2:1-6). Therefore, a POSA would have further reason to expect to be able to

successfully formulate an aqueous liquid ophthalmic preparation of bromfenac containing tyloxapol because Fu indicates that stable aqueous preparations of NSAIDs can be made using a surfactant (Octoxynol 9) that is closely related to (and known to be interchangeable with) tyloxapol.

5. Claims 2, 8 and 14—Sodium Sulfite

81. Claims 2, 8, and 14, depend directly from claims 1, 7, and 13, and recite “wherein the aqueous liquid preparation further consists of sodium sulfite.” (EX1001, 11:43-45, 12:13-15, and 12:51-53). Ogawa’s Example 6 includes sodium sulfite. (EX1004, 10:5-18). The example in Ogawa discloses this limitation, and for the same reasons discussed above for independent claims 1, 7 and 13, these claims would have been obvious over the prior art.

82. Furthermore, the ’813 patent specification refers to sodium sulfite as one of many conventional excipients. (EX1001, 5:55-56). For the same reasons described above for claims 1, 7, and 13, a POSA would also have had a reasonable expectation of success that the resulting preparations, as 2, 8, and 14 of the ’813 patent, would work as ophthalmic preparations.

6. Claims 3 and 15—Bromfenac Sodium Salt

83. Claims 3 and 15 depend directly from claims 1 and 13, respectively, and recite the use of 2-amino-3-(4-bromobenzoyl)phenyl acetic acid *sodium salt*. (EX1001, 11:46-48; 12:54-56). Claims 6, 10, 12, 16, 18, 21, and 23, which depend

directly or indirectly from claims 1, 7, and 13, also recite the sodium salt of bromfenac, in addition to other limitations discussed below.

84. This further limitation is disclosed in the example in Ogawa. Example 6 of Ogawa contains the sodium salt of bromfenac. (EX1004, 10:8-9). In fact, every working example in Ogawa discloses the sodium salt form of bromfenac. Further, other prior art references which make up the knowledge of a POSA at the relevant time, including Hara, for example, expressly disclose the sodium salt of bromfenac. (EX1002, Title, 2:1:2, 3:1:2). As such, a POSA would have a reasonable expectation of selecting the sodium salt of bromfenac in formulating an aqueous ophthalmic formulation containing bromfenac.

7. Claims 4, 6, 10, 12, 16, 18, 21, and 23—Concentrations

85. Claims 4, 6, 10, 16, and 21 depend directly from claims 1, 7, or 13, except claim 21 which depends on claim 20 further discussed below. Claims 4, 6, 10, 16, and 21 recite a tyloxapol concentration “from about¹⁴ 0.01 w/v % to about

¹⁴ I understand that “about” as used in the claims of the ’813 patent, a POSA, in light of the specification using the broadest reasonable construction would interpret “about 0.01 w/v % to about 0.05 w/v %” to include a w/v % between 0.005-0.054 w/v %. These percentage values are derived from the weights and volumes measured to prepare the aqueous preparations.

0.05 w/v %.” Claim 12 depends on claim 7 and recites “the concentration of tyloxapol is about¹⁵ 0.02 w/v %.” Claim 18 depends on claim 12 and recites “the concentration of tyloxapol is from about¹⁶ 0.02 w/v % to about 0.05 w/v %.” Sallmann’s Example 2—formulation of diclofenac potassium eye drops (0.05%) containing: 1.0 mg/ml tyloxapol. (EX1009, 8:10). Accordingly, Sallmann Example 2 discloses a tyloxapol concentration of 0.1 w/v %.

86. Claims 6 and 18 depend directly from claims 1 and 13, respectively, and provides that bromfenac is present in the claimed preparations as its sodium salt at a concentration of “about¹⁷ 0.02 w/v % to about 0.1 w/v %.” Claims 10, 12, 16, 21, and 23 depend directly from claims 7 or 13, except claim 21 which depends on claim 20 further discussed below. Claims 10, 12, 16, 21, and 23 provide that bromfenac is present in the claimed preparations as its sodium salt at a

¹⁵ A POSA would understand “about 0.02 w/v %” to include 0.015-0.024 w/v %.

¹⁶ A POSA would understand “about 0.02 w/v % to about 0.05 w/v %” to include 0.015-0.054 w/v %.

¹⁷ As discussed above in footnote 14, a POSA would understand “about 0.02 w/v % to about 0.1 w/v %” to include 0.015-0.14 w/v %.

concentration of “about¹⁸ 0.05 w/v % to about 0.1 w/v %.” Ogawa discloses that the active ingredient can be in the range from 0.001% to about 10% (EX1004, 4:42-46). Ogawa’s Example 6 discloses the ophthalmic solution contains 0.1 g of bromfenac sodium monohydrate in 100 ml.¹⁹ (EX1001, 10:5-18).

87. As described above with respect to claim 1, a POSA would have had reasons to combine Ogawa’s disclosure of an aqueous liquid ophthalmic formulation containing the acidic NSAID, bromfenac, BAC, and polysorbate 80 with the disclosure of Sallmann to arrive at the aqueous liquid ophthalmic preparations of claims 1, 7, and 13. A POSA reading Ogawa and Sallmann would have had a reason to combine the disclosures as claimed because Ogawa teaches an aqueous liquid ophthalmic formulation of 0.1% bromfenac sodium salt that contains the non-ionic surfactant, polysorbate 80, and Sallmann teaches that the non-ionic surfactant, tyloxapol, is preferred in ophthalmic preparations of the NSAID, diclofenac. (EX1009, 4:62). As also described above, the ophthalmic formulation disclosed in Ogawa’s Example 6 contains 0.1 w/v % of bromfenac

¹⁸ A POSA would understand “about 0.05 w/v % to about 0.1 w/v %” to include 0.045-0.14 w/v %.

¹⁹ 0.1 g of sodium bromfenac monohydrate in 100 ml of the formulation is equivalent to 0.1 w/v % of sodium monohydrate.

sodium monohydrate. (EX1004, 10:5-18). Ogawa discloses that the concentration of the active ingredient in the disclosed formulations can be in the range of about 0.001% to about 10%. (EX1004, 4:42-45). Thus, Ogawa teaches the concentration of bromfenac sodium that is encompassed by claims 6, 10, 12, 16, 18, 21, and 23 and that the concentration of bromfenac sodium can be optimized.

88. In addition, a POSA would have known that the concentration of an active pharmaceutical ingredient, such as bromfenac, is routinely optimized, and would also have had a reasonable expectation of success in optimizing the bromfenac concentration to arrive at the preparations as claimed in claims 6, 10, 12, 16, 18, 21, and 23 of the '813 patent, and that the resulting preparations would work as ophthalmic preparations.

89. Other prior art references which make up the knowledge of a POSA at the relevant time would have further motivated a POSA to combine the teachings of Ogawa and Sallmann, so as to arrive at the preparations recited in claims 6, 10, 12, 16, 18, 21, and 23 of the '813 patent. For example, the additional sodium salt limitation of claims 6, 10, 12, 16, 18, 21, and 23 are described in Hara. (EX1002, 3:1:2). Furthermore, Sallmann states that the concentration of the active ingredient in the disclosed formulations can be in the range of approximately 0.000001% to approximately 5.0% by weight, preferably from approximately 0.001% to approximately 1.0% by weight, or more preferably from approximately 0.01% to

approximately 0.5% by weights, and most preferably in the range of from 0.025% to 0.1% by weight. (EX1009, 3:60-66.). Thus, Hara teaches a specific concentration of bromfenac sodium that is encompassed by claims 6, 10, 12, 16, 18, 21, and 23, and Sallmann teaches that the concentration of an NSAID can and should be optimized.

90. A POSA would have had a reason to rely on its knowledge of the art, as disclosed in Hara, for example, because Sallmann teaches an aqueous liquid ophthalmic formulation of diclofenac formulated with 0.1 w/v % tyloxapol and benzalkonium chloride, and Hara teaches that 0.1 w/v % bromfenac sodium hydrate is broadly applicable for treatment of various ophthalmic conditions, as compared to diclofenac. And for the same reasons described in for claim 1 above, a POSA would also have had a reasonable expectation of success that the preparations as claimed in claims 6, 10, 12, 16, 18, 21, and 23 patent would work as ophthalmic preparations.

91. Although the tyloxapol concentration utilized in Sallmann's Example 2 is 0.1 w/v % and does not overlap with the claimed tyloxapol range of 0.01 w/v % to 0.05 w/v % set forth in claims 4, 6, 10, 16, and 21, nor with the claimed tyloxapol concentration of 0.02 w/v % set forth in claim 12, nor with the claimed tyloxapol range of 0.02 w/v % to 0.05 w/v % set forth in claim 18, the ranges are

close enough that a POSA would have expected such formulations to have the same properties.

92. Further, a POSA would have known that the concentration of an additive, such as tyloxapol, is routinely optimized, and would also have had a reasonable expectation of success in optimizing the tyloxapol concentration to arrive at the preparations as claimed in claims 4, 6, 10, 12, 16, 18, and 21 of the '813 patent.

8. Claims 6, 12, 18, and 23—Additional Additives

93. Claims 6, 12, 18, and 23 depend directly or indirectly from claims 1, 7, and 13, and contain the further limitation that the stable aqueous preparation consists of bromfenac as its sodium salt or a hydrate selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate at a concentration from about 0.02 w/v % to about 0.1 w/v % or from about 0.05 w/v % to about 0.1 w/v %, tyloxapol at a concentration from about 0.01 w/v % to about 0.05 w/v %, about 0.02 w/v %, or about 0.02 w/v % to about 0.05 w/v %, and various additives, including boric acid, sodium tetraborate, EDTA sodium salt, polyvinylpyrrolidone, and sodium sulfite. It is my understanding that when a claim contains the phrase “consists of,” it excludes any element, step, or ingredient not specified in the claim.

94. Claims 6 and 18 recite the concentration of bromfenac sodium salt is “about 0.02 w/v % to about 0.1 w/v %.” (EX1001, 11:60-62, 13:2-5). Claims 12

and 23 recite the concentration of bromfenac sodium salt is “about 0.05 w/v % to about 0.1 w/v %.” (EX1001, 12:35-38, 14:9-11). As discussed in detail with respect to claims 6, 10, 12, 16, 18, 21, and 23 above, Ogawa discloses that the concentration of the active ingredient in the disclosed formulations can be in the range of about 0.001% to about 10%. (EX1004, 4:42-45). Ogawa Example 6 contains bromfenac sodium monohydrate -0.1g in 100 ml.²⁰ (EX1004, 10:5-18). In this way, Ogawa teaches the concentration of bromfenac sodium that is encompassed by claims 6, 12, 18, and 23, and that the concentration of bromfenac can and should be optimized. Further, claims 12-18 recite the bromfenac hydrate “is at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate,” which is met by Ogawa’s Example 6 because it discloses the monohydrate of bromfenac sodium. (EX1004, 10:5-18).

95. Claims 6, 12, and 18 depend directly on claims 1, 7, and 13, respectfully. Claim 6 requires the tyloxapol concentration to be “about 0.01 w/v % to about 0.05 w/v %.” Claim 12 requires the tyloxapol concentration to be “about 0.02 w/v %.” Claim 18 requires the tyloxapol concentration to be “about 0.02 w/v % to about 0.05 w/v %.”). As discussed in detail with respect to claims 6, 10, 12,

²⁰ 0.1 g of sodium bromfenac monohydrate in 100 ml of the formulation is equivalent to 0.1 w/v % of sodium bromfenac monohydrate.

16, 18, 21, and 23 above, Sallmann's Example 2 discloses a formulation of diclofenac potassium eye drops (0.05%) containing 1.0 mg/ml tyloxapol. (EX1009, 8:10). Accordingly, Sallmann Example 2 discloses a tyloxapol concentration of 0.1 w/v %. As discussed above, the concentration disclosed by Sallmann Example 2 is close enough to the claimed ranges that a POSA would have expected such formulations to have the same properties. Further, a POSA would have known that the concentration of an additive, such as tyloxapol, is routinely optimized, and would also have had a reasonable expectation of success in optimizing the tyloxapol concentration to arrive at the preparations as claimed in claims 6, 12, and 18 of the '813 patent.

96. In addition to (a) bromfenac sodium salt and (b) tyloxapol discussed above, Claims 6, 12, 18, and 23 further require (c) boric acid, (d) sodium tetraborate (borax), (e) EDTA sodium salt, (f) polyvinylpyrrolidone (PVP), (g) sodium sulfite, and (h) water. (EX1001, 11:57-59, 12:33-35, 13:1-3, 14:6-8). Example 6 of Ogawa discloses an ophthalmic formulation with sodium bromfenac monohydrate, boric acid and sodium tetraborate (a buffer system), EDTA sodium salt (a chelating agent) (EDTA and edetate are synonyms), BAC (a preservative), polysorbate 80 (a surfactant), PVP (a thickener), sodium sulfite (a stabilizer), and water. (EX1004, 10:5-18). Thus, by substituting tyloxapol from Sallmann's Example 2, for polysorbate 80 in Ogawa's Example 6, as discussed above for

claim 1, a POSA would arrive at the preparations recited in claims 6, 12, 18, and 23. (EX1009, 8:1-10).

97. Furthermore, the '813 patent specification refers to boric acid, sodium tetraborate, sodium edetate, polyvinylpyrrolidone, and sodium sulfite as conventional excipients. (EX1001, 5:43-60). Therefore, a POSA would have had a reason to further include these conventional ingredients into the ophthalmic preparations of bromfenac described in Ogawa's Example 6. Also, the use of preservatives is not mandatory, as suggested by Ogawa, thus a POSA would have found it obvious to add or remove a preservative such as BAC from an ophthalmic preparation like the one described in Ogawa's Example 6. (EX1004, 4:21-26, 4:64-65). Indeed, the ophthalmic solution described in Ogawa's Example 5 does not contain BAC or any other preservatives. (EX1004, 9:60-10:3).

98. A POSA reading Ogawa and Sallmann would have had reason to combine their disclosures because Ogawa teaches an aqueous liquid ophthalmic formulation of bromfenac that contains the non-ionic surfactant polysorbate 80, boric acid, sodium tetraborate, sodium edetate, BAC, polyvinylpyrrolidone, and sodium sulfite, and Sallmann teaches that the non-ionic surfactant, tyloxapol, is one of the preferred surfactants in ophthalmic preparations of the NSAID, diclofenac. (EX1004, 10:5-18; EX1009, 4:62). For the same reasons described above for claim 1, a POSA would also have had a reasonable expectation of

success that the resulting preparations, as 6, 12, 18, and 23 of the '813 patent, would work as ophthalmic preparations.

99. Other prior art references which make up the knowledge of a POSA at the relevant time, such as Hara, provide further motivation for a POSA to combine the teachings of Ogawa and Sallmann to arrive at the preparations recited in claims 6, 12, 18, and 23. The additional additives contained in claims 6, 12, 18, and 23 are also taught in Sallmann, which discloses the use of a borate as a buffer, polyvinylpyrrolidone as a carrier, sodium hydrogen sulfite as an antioxidant, disodium edetate as a chelating agent, and HCl or NaOH as pH controlling agents. (EX1009, 8:1-15, 4:23-30, 5:8-10, 5:47-53, 10:22, 14:14). A POSA would have also known that excipients such as boric acid, sodium tetraborate, EDTA sodium salt, polyvinylpyrrolidone, and sodium sulfite were routinely used in ophthalmic formulation by 2003. Further, a POSA would have expected sodium edetate and disodium edetate, both disclosed in Ogawa, to have similar properties as a chelating agent. (EX1004, 4:33-35, 9:32, 10:12). Therefore, a POSA would have had a reason to further include these conventional ingredients into the ophthalmic preparations of bromfenac. A POSA would also have had a reasonable expectation of success that the preparations as claimed in claims 6, 12, 18, and 23 of the '813 patent would work as ophthalmic preparations.

9. Claims 5, 11, 17, and 22—pH Ranges

100. Claims 5, 11, 17, and 22 depend directly or indirectly from Claims 1, 7, and 13, and recite the pH ranges for the claimed preparations is “from about²¹ 7.5 to about 8.5.” (EX1001, 11:51-53, 12:26-27, 12:61-62, 13:22-24).

101. Ogawa’s Example 6 discloses a pH of 8. (EX1004, 10:18). Ogawa also discloses a pH from about 7.5 to about 8.5. (EX1004, 3:48-52). A POSA reading Ogawa and Sallmann would have had reason to combine their disclosures because Ogawa teaches that the pH of the aqueous ophthalmic preparations of bromfenac sodium and the non-ionic surfactant polysorbate 80 is 8.0, and Sallmann teaches that the non-ionic surfactant, tyloxapol, is preferred in ophthalmic preparations of the NSAID, diclofenac, at the more preferred pH range of 6.8-8.1 and describes examples all with pH between 7.80 and 7.98. (EX1009, 4:62, 5:14-16, Examples 14-19 at 12:38-14:42).

²¹ I understand that “about” as used in the claims of the ’813 patent, a POSA, in light of the specification using the broadest reasonable construction would interpret the pH range of “about 7.5 to about 8.5” to include a pH between 7.0 and 9.0.

102. Other prior art references which make up the knowledge of a POSA at the relevant time, such as Hara, expressly disclose a bromfenac sodium preparation having a pH of 8.0-8.6. (EX1002, 3:1:2).

103. Further a POSA would know that about 7.5 to about 8.5 would be an acceptable pH range for an ophthalmic preparation. And for the same reasons described above for claims 1, 7, and 13, a POSA would also have had a reasonable expectation of success that the resulting preparations as claimed in claims 5, 11, 17, and 22 would work as ophthalmic preparations.

10. Claims 9, 19, and 20—Stability

104. Claim 9 depends directly from claim 7, and claim 20 depends indirectly from claim 13. Both claims 9 and 20 contain the further limitation that “the stable aqueous liquid preparation is characterized in that greater than about 92% of the original amount of the first component remains in the preparation after storage at about 60° C. for 4 weeks.” (EX1001, 12:15-19, 13:11-15). Claim 19 depends directly from claim 13 and contains the limitation that “the stable aqueous liquid preparation is characterized in that greater than about 90% of the original amount of the first component remains in the preparation after storage at about 60° C. for 4 weeks.” (EX1001, 13:7-10).

105. As explained in detail with respect to claims 1, 7, and 13, a POSA would have had reasons to combine Ogawa’s disclosure of an aqueous liquid

ophthalmic formulation containing the acidic NSAID bromfenac and polysorbate 80 with the disclosure of Sallmann to arrive at the aqueous liquid ophthalmic formulations of claims 1, 7, and 13.

106. Further, as previously discussed with respect to independent claim 7, Table 11 of Ogawa describes that Example 6 Ophthalmic Solution contained 100% of the original amount of bromfenac sodium after storage for 4 weeks at 60° C. (EX1004, 10:50-57, 14:45-50). Sallmann also states “[a]nother preferred solubilizer is tyloxapol. The concentration used depends especially on the concentration of the active ingredient. The amount added is typically sufficient to solubilize the active ingredient.” (EX1009, 4:62-65). Further, Sallmann Example 2 contains 1.0 mg/ml of tyloxapol, corresponding to 0.1 w/v %. (EX1009, 8:1-10). The amount of tyloxapol disclosed in Sallmann Example 2 is within the general disclosure of the '813 patent, which teaches a tyloxapol minimum content of about 0.01 w/v % and a maximum content of about 0.5 w/v %. (EX1001, 5:20-25). Therefore, it is my opinion that a POSA would have a reasonable expectation of success in formulating a stable aqueous ophthalmic formulation containing bromfenac wherein the amount of bromfenac remaining after storage at 60° C for 4 weeks would be greater than 90% or 92%.

11. Claims 24-26—No Preservative

107. Claims 24-26 depend directly from claims 1, 7, and 13, respectively, and contain the further limitation that the aqueous liquid preparation does not include any preservative. (EX1001, 14:12-19).

108. Ogawa's Example 6 also contains BAC. Ogawa, however, teaches that "[i]n preparing the ophthalmic compositions according to the invention . . . a microbicidal agent or preservative . . . may be added to the compositions in accordance with the general practice" and that "preservatives can be used." (EX1004, 4:21-26, 4:64-65). Because the use of preservatives is not mandatory, a POSA would have found it obvious to add or remove a preservative such as BAC from an ophthalmic preparation like the one described in Ogawa's Example 6. Indeed, the ophthalmic solution described in Ogawa's Example 5 does not contain BAC or any other preservatives. (EX1004, 9:60-10:3).

109. Sallmann also provides that preservatives are among the customary pharmaceutically acceptable excipients and additives known to a POSA. (EX1009, 4:4-10). Sallmann also provides that preservatives are added to ophthalmic compositions where appropriate. (EX1004, 4:21-22). Accordingly, Sallmann also provides that the use of preservatives is not mandatory, thus a POSA would have found it obvious to add or remove a preservative such as BAC from an ophthalmic preparation like the one described in Ogawa's Example 6.

12. Claim 27—Additional Additives

110. Claims 27 depends directly from claim 1 and contain the further optional limitation that the formulation further consist of one or more additives such as buffers, thickeners, stabilizers, chelating agents, and pH controlling agents. (EX1001, 14:20-23).

111. A POSA would have also known that excipients such as buffers, thickeners, stabilizers, chelating agents, and pH controlling agents were routinely used in ophthalmic formulation by 2003. The '813 patent also shows these additives were considered as conventional additives and excipients. (EX1001, 5:43-60). Ogawa and Sallmann also show these additives were conventional and well known. (EX1004, 3:43-45, 3:48-53, 3:62-67, 4:23-24; EX1009, 4:4-10, 4:18-21, 5:50-56, 8:9).

112. Therefore, a POSA would have had a reason to further include these conventional ingredients into the ophthalmic preparations of bromfenac. A POSA would also have had a reasonable expectation of success that the preparations as claimed in claim 27 of the '813 patent would work as ophthalmic preparations.

113. Accordingly, POSA would have had a reason to further include these conventional ingredients into the ophthalmic preparations of bromfenac described in Ogawa's Example 6. A POSA would also have had a reasonable expectation of success that the resulting preparations would work as ophthalmic preparations.

C. Obviousness Ground 2 – Ogawa and Sallmann and Fu

114. In the alternative, a POSA would have had a reason to combine the disclosures of Ogawa and Sallmann further in view of Fu to arrive at the claimed inventions with a reasonable expectation of success.

115. I have been informed that Australian Patent No. AU-B-22042/88 (“Fu”) (EX1011) to Cherng-Chyi Roger Fu et al., titled “Preservative System for Ophthalmic Formulations,” issued on August 13, 1992, qualifies as prior art to the challenged claims of the ’813 patent. (EX1011). Fu describes an experiment (Example 5) of creating formulations of ketorolac and BAC with three different surfactants: Octoxynol 40, polysorbate 80, and Myrj 52. (EX1011, 20:23-27). The stability of the formulations was measured by observing the solutions after a period of time, where clarity indicated stability. (EX1011, 20:11-17).

	<u>Octoxynol 40</u>		<u>Tween 80</u>		<u>Myrj 52</u>	
	0.004%	0.02%	0.0035%	0.01%	0.0015%	0.01%
<u>1 month</u>						
60°C	clear	clear	clear	clear	clear	clear
40°C	clear	clear	very turbid	very turbid	turbid	turbid
RT	clear	clear	turbid	turbid	clear	clear
4-40°C	clear	clear	turbid	turbid	clear	clear
<u>5 month</u>						
60°C	clear	clear	clear	clear	clear	clear
40°C	clear	clear	turbid	turbid	turbid	turbid
RT	clear	clear	turbid	turbid	turbid	turbid

(EX1011, 21:1-14). The experiment showed that Octoxynol 40 was superior to the other two and that the presence of turbidity suggested the inability to solubilize the precipitate formed between the ketorolac moiety and BAC. (EX1011, 21:16-22).

1. Claims 1, 7, and 13

116. The disclosures of Ogawa and Sallmann are discussed above with respect to Ground 1.

117. The teachings in Fu provide additional motivation for a POSA to combine the disclosures of Ogawa and Sallmann further in view of Fu to arrive at the claimed inventions with a reasonable expectation of success. Specifically, Fu provides additional motivation to substitute tyloxapol, as disclosed in Sallmann and Fu, instead of the polysorbate 80 disclosed in Ogawa's Example 6.

118. Fu shows that it was known prior to January 21, 2003 that acidic NSAIDs (such as bromfenac) containing an ionizable carboxylic acid group form complexes with quaternary ammonium preservatives, such as BAC, in ophthalmic formulations. (EX1011, 3:26-4:5, 5:13-21). These complexes were known to precipitate out of ophthalmic formulations, which is problematic because it (1) lessens the preservative efficacy of the preservative (*i.e.* BAC), and (2) reduces the availability of the active ingredient (*i.e.* the NSAID). (EX1011, 5:1-7, 5:13-21).

119. Fu also shows that it was known prior to January 21, 2003 that choosing an appropriate surfactant would resolve this issue. For example, Fu

disclosed stable aqueous preparations containing acidic NSAIDs formulated with both BAC and non-ionic surfactants closely related to tyloxapol, Octoxynol 40. (EX1011, 18:5-28, 20:9-21:27, Examples 2 and 5).

120. Fu indicated that non-ionic surfactants in the ethoxylated octylphenol class, such as Octoxynol 9 and Octoxynol 40, can stabilize aqueous liquid ophthalmic NSAID preparations that contained BAC, even in the absence of PVP or a sulfite. (EX1011, 12:1-12, Example 5). Importantly, preservative efficacy in the preparations of Fu was maintained throughout the 2 year shelf-life. (EX1011, Example 5). Therefore, it was known, prior to 2003, that ethoxylated octylphenol surfactants could eliminate instability caused by the interaction of an acidic NSAID with BAC.

121. By January 2003, tyloxapol was a known non-ionic surfactant used to stabilize aqueous ophthalmic preparations of NSAIDs and other acidic drugs. Structurally, tyloxapol is an oligomeric form of Octoxynol 9 (Triton X-100), which Fu described as an example of a preferred/useful stabilizer of aqueous ophthalmic formulation of NSAIDs and BAC in the 1980's. (EX1011, 12:1-11).

122. Accordingly, Fu provides additional motivation for a POSA to choose ethoxylated octylphenol surfactants or similar non-ionic surfactants for formulations containing a NSAID and BAC. One such surfactant at the time was

tyloxapol, which Sallmann shows was a preferred surfactant for aqueous ophthalmic formulations. (EX1009, 4:62).

123. A POSA would also have had a reasonable expectation of success for an aqueous liquid preparation of bromfenac formulated with tyloxapol instead of polysorbate 80, as suggested by Sallmann and Fu. Fu indicates that ethoxylated octylphenol surfactants, such as Octoxynol 9 or Octoxynol 40, can stabilize aqueous liquid preparations of NSAIDs and BAC. (EX1011, 12:1-11, Example 5). A POSA would have known that tyloxapol is an oligomer of Octoxynol 9, and that both are ethoxylated octylphenol surfactants. (EX1019, 1:1:1-2:1:2; EX1020, 8:2:1). In fact, tyloxapol (Triton WR1339) and Octoxynol 9 (Triton X-100) have been used interchangeably in manufacturing ophthalmic preparations. (EX1049, 2:1-6). Therefore, a POSA would have further reason to expect to be able to successfully formulate an aqueous liquid ophthalmic preparation of bromfenac containing tyloxapol because Fu indicates that stable aqueous preparations of NSAIDs can be made using a surfactant (Octoxynol 9) that is closely related to (and known to be interchangeable with) tyloxapol.

2. Claims 4, 6, 10, 12, 16, 18, and 21—Tyloxapol Concentrations

124. Claims 4, 6, 10, 12, 16, 18, and 21 depend directly or indirectly from claims 1, 7, and 13. Claims 4, 6, 10, 16, and 21 recite a tyloxapol concentration of about 0.01 to about 0.05 w/v %, claim 12 recites a tyloxapol concentration of about

0.02 w/v %, and claim 18 recites a tyloxapol concentration of about 0.02 to about 0.05 w/v %.

125. In addition, a POSA would have known that the concentration of a surfactant, such as tyloxapol, is routinely optimized. For example, Sallmann states the concentration of tyloxapol depends on the concentration of the active ingredient and that the amount is typically enough to solubilize the active ingredient. (EX1009, 4:62-65).

126. Fu provides additional motivation for a POSA to use tyloxapol at a concentration within the claimed ranges. Specifically, Fu discloses a formulation with 0.02 w/v % of Octoxynol 40 which was superior to other surfactants. (EX1011, 21:1-18). Thus, Fu teaches a specific concentration of ethoxylated octylphenol surfactants that is encompassed by claims 4, 6, 10, 12, 16, 18, and 21, and Sallmann teaches that the concentration of tyloxapol should be optimized.

127. A POSA would also have had a reasonable expectation of success in optimizing the tyloxapol concentration to arrive at the preparations as claimed in claims 4, 6, 10, 12, 16, 18, and 21 of the '813 patent, and that the resulting preparations would work as ophthalmic preparations.

D. Obviousness Ground 3 – Ogawa and Sallmann and Yasueda

128. In the alternative, a POSA would have had a reason to combine the disclosures of Ogawa and Sallmann further in view Yasueda to arrive at the claimed inventions with a reasonable expectation of success.

129. I have been informed that U.S. Patent No. 6,274,609 (“Yasueda”) (EX1012) to Shinichi Yasueda *et al.*, titled “Aqueous Liquid Pharmaceutical Composition Containing as Main Component Benzopyran Derivative,” issued on August 14, 2001, qualifies as prior art to the challenged claims of the ’813 patent. (EX1012). Yasueda describes an experiment (Experiment 4) where the stability of pranlukast solutions was measured by HPLC to calculate the residual rate after 2 weeks at 60° C. (EX1012, 6:47-55). Various surfactants including polysorbate 80 and tyloxapol were studied.

TABLE 4

Component	Formulation					
	A	B	C	D	E	F
pranlukast	0.1 g	0.1 g	0.1 g	0.1 g	0.1 g	0.1 g
polysorbate 80	—	—	—	4.0 g	4.0 g	4.0 g
Tyloxapol	4.0 g	4.0 g	—	—	—	—
HCO-60*	—	—	4.0 g	—	—	—
boric acid	—	1.9 g	—	—	—	—
BHT**	—	—	—	—	0.01 g	—

TABLE 4-continued

Component	Formulation					
	A	B	C	D	E	F
sodium edetate	—	—	—	—	—	0.01 g
sodium di-hydrogen phosphate	0.1 g	—	0.1 g	0.1 g	0.1 g	0.1 g
benzalkonium chloride	0.005 g	—	—	—	—	—
0.1 N sodium hydroxide	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
sterilized purified water	up to total 100 ml	up to total 100 ml	up to total 100 ml	up to total 100 ml	up to total 100 ml	up to total 100 ml
pH	7.0	7.0	7.0	7.0	7.0	7.0

*polyoxyethylene hydrogenated castor oil 60

**butylated hydroxytoluene

(EX1012, 6:55-7:19).

130. The experiment showed that the formulation with tyloxapol has better stability compared to the formulation with polysorbate 80, and that when tyloxapol was used the residual rate of pranlukast was 99.5% on average. (EX1012, 7:25-42).

TABLE 5

	Residual rate (%)					
	A	B	C	D	E	F
Immediately after preparation	100.0	100.0	100.0	100.0	100.0	100.0
After two weeks	99.6	99.4	98.9	85.0	97.5	95.1

(EX1012, 7:25-34).

1. Claims 1, 7, and 13

131. The disclosures of Ogawa and Sallmann are discussed above with respect to Ground 1.

132. The teachings in Yasueda provide additional motivation for a POSA to combine the disclosures of Ogawa and Sallmann further in view Yasueda to arrive at the claimed inventions with a reasonable expectation of success.

133. Yasueda shows that it was known prior to January 21, 2003 that tyloxapol, as a surfactant and solubilizing agent, stabilized negatively charged drugs in aqueous preparations better than polysorbate 80. Experiment 4 of Yasueda demonstrated that tyloxapol was better than polysorbate 80 at solubilizing and stabilizing pranlukast in an ophthalmic solution. (EX1012, 6:55-7:43, Tables 4 and 5). Specifically, Yasueda demonstrated that the amount of pranlukast in the solution with polysorbate 80 decreased by 15% after two weeks of storage, and only by 0.5%, on average, during the same time period when using tyloxapol. (EX1012, 6:55-7:43, Tables 4 and 5). Therefore, Yasueda demonstrated that tyloxapol increased the stability of pranlukast by, on average, a factor of 30.²² Yasueda also noted that when using polysorbate 80, additional stabilizers were needed to achieve drug content in solution greater than 95%. (EX1012, 7:37-43).

²² See supra n. 11.

134. Accordingly, Yasueda provides additional motivation for a POSA to choose tyloxapol as a non-ionic surfactant over polysorbate 80 in developing an aqueous liquid ophthalmic formulation to maintain the stability of the acidic drug.

135. A POSA would also have had a reasonable expectation of success for developing an aqueous liquid preparation where tyloxapol was substituted with polysorbate 80, as suggested by Sallmann and Yasueda, to the formulation disclosed in Ogawa. Ogawa provides working examples of bromfenac preparations formulated with polysorbate 80 and a POSA would have further reason to expect to be able to successfully formulate an aqueous liquid ophthalmic preparation of bromfenac containing tyloxapol, because Yasueda indicates that tyloxapol is superior to polysorbate 80 in solubilizing acidic ophthalmic drugs. (EX1004, 10:5-18; EX1012, Tables 4 and 5).

2. Claims 4, 6, 10, 12, 16, 18, and 21—Tyloxapol Concentrations

136. Claims 4, 6, 10, 12, 16, 18, and 21 depend directly or indirectly from claims 1, 7, and 13. Claims 4, 6, 10, 16, and 21 recite a tyloxapol concentration of about 0.01 to about 0.05 w/v %, claim 12 recites a tyloxapol concentration of about 0.02 w/v %, and claim 18 recites a tyloxapol concentration of about 0.02 to about 0.05 w/v %.

137. In addition, a POSA would have known that the concentration of a surfactant, such as tyloxapol, is routinely optimized. For example, Sallmann states

the concentration of tyloxapol depends on the concentration of the active ingredient and that the amount is typically enough to solubilize the active ingredient. (EX1009, 4:62-65).

138. Yasueda provides additional motivation for a POSA to use tyloxapol at a concentration within the claimed ranges. Specifically, Yasueda discloses a surfactant concentration range that is preferably 0.01 to 0.2 w/v % for an aqueous suspension. (EX1012, 3:10-15). Yasueda also discloses a surfactant concentration range that is preferably 2 to 4 w/v % for an aqueous solution. (EX1012, 3:1-5). Thus, Yasueda teaches a specific concentration of surfactants that is encompassed by claims 4, 6, 10, 12, 16, 18, and 21, and Sallmann teaches that the concentration of tyloxapol should be optimized.

139. Sallmann also discloses that the ophthalmic composition can be a solution, suspension, or other forms. (EX1009, 3:57-60). Thus both preferred surfactant concentrations disclosed in Yasueda could be applied to Sallmann.

140. A POSA would also have had a reasonable expectation of success in optimizing the tyloxapol concentration to arrive at the preparations as claimed in claims 4, 6, 10, 12, 16, 18, and 21 of the '813 patent, and that the resulting preparations would work as ophthalmic preparations.

VIII. No Unexpected Results Over the Closest Prior Art

141. I understand in the course of prosecution of the family members of the '813 patent, Senju alleged that the claimed aqueous liquid preparations of bromfenac exhibit unexpected results. Specifically, Senju alleged during prosecution of the '242 application that "there is no suggestion to avoid degradation of acidic drugs, such as bromfenac, by using tyloxapol" (EX1023, 8) and applicant "surprisingly found that the degradation of bromfenac could be avoided by specifically including tyloxapol in the preparation." (EX1025, 4). Senju also alleged during prosecution of the '006 application that tyloxapol unexpectedly stabilized aqueous liquid preparations of bromfenac in comparison with preparations containing polysorbate 80. (EX1015, 4). Senju also alleged during prosecution of the '006 application that "present inventors have found that tyloxapol has an unexpected stabilizing effect on an aqueous solution of bromfenac in comparison to polysorbate 80." (EX1015, 4). I have been asked to consider Senju's arguments and evidence, and opine as to whether, as of January 21, 2003, the alleged properties of the claimed preparations would have been unexpectedly superior compared to other aqueous liquid preparations known at the time, such as the liquid preparations of NSAIDs disclosed by Ogawa. Having reviewed Senju's arguments and evidence, I conclude that the results achieved with the claimed

preparations would not have been unexpected in view of the other previously-known preparations.

A. Tyloxapol's stabilization of an aqueous ophthalmic bromfenac preparation is not unexpected in view of the prior art

142. The stability of the claimed aqueous liquid preparations of bromfenac is not unexpectedly superior compared with the aqueous liquid ophthalmic preparation of bromfenac disclosed in Ogawa. As I discussed above, Ogawa discloses stable aqueous compositions of bromfenac containing BAC and the non-ionic surfactant polysorbate 80. (EX1004, 8:3-14). As such, Ogawa is the closest prior art reference because it contains the most limitations in common with the claimed invention, compared to any other prior art. I have considered—and disagree with—Senju's assertion that "there is no suggestion to avoid degradation of acidic drugs, such as bromfenac, by using tyloxapol," (EX1023, 8), that it would have been surprising that "the degradation of bromfenac could be avoided by specifically including tyloxapol in the [ophthalmic] preparation," (EX1025, 4), and that "tyloxapol has an unexpected property in stabilizing an aqueous solution of bromfenac in comparison with polysorbate 80." (EX1015, 4; EX1015, 7). The stabilization achieved in the claimed aqueous liquid preparations would not have been unexpected when compared with Ogawa's aqueous liquid preparation of bromfenac and in view of the general state of the art.

143. First, as discussed above, a POSA would have known that aqueous liquid ophthalmic preparations containing an NSAID and BAC could be stabilized by including a non-ionic surfactant in the preparation. (EX1004, Experimental Examples 4 and 6, 10:5-18; EX1022, 10:1-8, 4:8-13). A POSA would have presumed that this stabilization could occur either by preventing the formation of the insoluble complex between BAC and the NSAID, or by solubilization of the BAC-NSAID complex and preventing it from precipitating.²³ In any event, a POSA would have known that a non-ionic surfactant would have stabilized an NSAID preparation.

²³ Non-ionic surfactants have been used to increase the solubility of NSAIDs (EX1050). Furthermore, nonionic surfactants were generally considered safe and useful for solubilizing poorly-soluble chemical entities. (EX1033, 5). Because the NSAID-BAC complexes were known to be insoluble, a POSA would have expected that non-ionic surfactants could also stabilize the aqueous preparations of the NSAID and BAC by solubilizing any such complexes. In fact, Fu suggested that nonionic ethoxylated octylphenol surfactants stabilize NSAID preparations by solubilizing the BAC-NSAID complex and preventing it from precipitating. (EX1011, 20:23-26; EX1050).

144. Fu indicated that non-ionic surfactants, such as Octoxynol 9 or Octoxynol 40, are useful for preparing stabilized aqueous liquid preparations of NSAIDs. (EX1011, 12:1-11, Example 5). And a POSA would have known that tyloxapol is an oligomeric form of Octoxynol 9. (EX1019, 1:1-2; EX1020, 8:2:1). In fact, tyloxapol and Octoxynol 9 had been used interchangeably in manufacturing ophthalmic preparations. (EX1049, 2:1-6). Therefore, a POSA would have expected that tyloxapol would have also stabilized an aqueous liquid preparation of bromfenac.

145. A POSA would have also expected that tyloxapol would be a better stabilizer of the aqueous preparations of bromfenac than polysorbate 80 because of its anticipated efficacy, as compared to polysorbate 80. Specifically, Fu suggested that formulations containing, for example, Octoxynol 9 and Octoxynol 40 “have proven to be stable,” while “[f]ormulations using surfactants other than the nonionic surfactants of the invention did not remain clear and were not stable.” (EX1011, 20:18-23). Among the nonionic surfactants tested by Fu, and shown to be unable to stabilize the aqueous liquid preparations of an NSAID was polysorbate 80. (EX1011, 20:9-21:27). In fact, Fu showed that polysorbate 80 was unable “to solubilize a precipitate formation between the ketorolac moiety and benzalkonium chloride,” while Octoxynol 40 “was superior to the other two surfactants.” (EX1011, 21:16-22). Further, the ophthalmic preparation of

ketorolac, BAC, and Octoxynol 40 maintained a 2 year shelf-life. (EX1011, 21:23-27). In addition, Fu suggested that Octoxynol 9 can be used in place of Octoxynol 40 in stabilizing the same aqueous liquid preparations of BAC and ketorolac. (EX1011, 12:1-12). And because tyloxapol is an oligomeric form of Octoxynol 9, a POSA would have also expected tyloxapol to stabilize a liquid preparation of an NSAID to a greater extent than polysorbate 80.

146. Furthermore, tyloxapol had been shown to stabilize aqueous liquid preparations of other acidic active pharmaceutical ingredients better than polysorbate 80. (EX1012, Tables 4 and 5). Specifically, Yasueda demonstrated that the use of tyloxapol as a solubilizing agent increased the stability of the acidic ophthalmic drug, pranlukast, by, on average, a factor of 30, relative to a formulation containing polysorbate 80. (EX1012, Tables 4 and 5). Yasueda also noted that when using polysorbate 80, additional stabilizers were needed to achieve greater than 95% drug stability. (EX1012, 7:37-43). As such, the stated superior stabilizing properties of tyloxapol over polysorbate 80 were known to a POSA by January 21, 2003. Therefore, there was nothing unexpected in tyloxapol's improved ability to stabilize bromfenac, as compared to polysorbate 80.

B. Scope of Stabilizing Effects

147. The purported unexpected stability of the claimed aqueous ophthalmic preparations of bromfenac, to the extent applicable to the claims of the '813 patent,

has not been demonstrated over the entire spectrum of preparations claimed in the '813 patent. I understand that unexpected results must occur over the entire claimed range of the preparations. However, a number of claimed liquid preparations of bromfenac would not be more stable than those disclosed in the prior art.

148. Specifically, Senju has not demonstrated, and is unlikely to be able to demonstrate, that the stability of aqueous bromfenac preparations is increased over the entire pH range claimed in the '813 patent. The pH of the claimed preparations of bromfenac is either undefined (claims 1-4, 6-10, 12-16, 18-21, and 23-27), or about 7.5 to about 8.5 (claims 5, 11, 17, and 22). But Senju's stability studies reporting the remaining rates of bromfenac in preparations with polysorbate 80 or tyloxapol were conducted only at one pH value, pH 7.0. (EX1001, Table 1). And when Senju compared the stability of bromfenac at pH 7.0, tyloxapol stabilized the aqueous liquid preparation of bromfenac better than polysorbate 80. [See Table 1 below.]

Table 1. Stability data of the bromfenac preparations reported by Ogawa (bromfenac is formulated with 0.3% polysorbate 80) and the '813 patent (bromfenac is formulated with 0.15% polysorbate 80 or 0.02% tyloxapol.)

pH	Ogawa[Exhibit 1004]	The '813 patent (EX1001)	
	% remaining after three weeks	% remaining after four weeks	
	0.3% Polysorbate 80	0.15% Polysorbate 80	0.02% Tyloxapol
7.0	54.2	51.3	89.6
~ 8 ²⁴	98.0	Not reported	92.6
9.0	99.0	Not reported	Not reported

149. However, Senju did not compare the stability of the bromfenac preparations at other pH values. And, as evidenced in Table 1 above, the aqueous liquid preparation of bromfenac and polysorbate 80 had 54.2%, 98%, and 99% of the original content of bromfenac after three weeks at pH 7, 8, and 9, respectively. (EX1004, Table 8). These results demonstrate that the stability of liquid

²⁴ Ogawa measured the remaining rate (or percent of the initial amount) of bromfenac at pH 8.0 (EX1004, Table 8), and the '813 patent measured the remaining rates of bromfenac at starting pH's 8.17, 8.15, and 8.16. (EX1001, Table 2).

preparations containing an NSAID and stabilized by a surfactant, is pH-dependent. Furthermore, these results show that, if compared at other claimed pH's, such as pH 8 or pH 9, polysorbate 80 would not be less effective than tyloxapol in stabilizing the claimed preparations. Therefore, the purported unexpected stability of the claimed preparations is not observed across the entire claimed pH range.

IX. No long-felt, unmet need existed for an ophthalmic NSAID preparation formulated with BAC

150. Senju cannot demonstrate that long-felt, but unmet need existed for an aqueous liquid preparation of an NSAID formulated with benzalkonium chloride for ophthalmic administration. Any such need was already met by aqueous ophthalmic formulations of NSAIDs known as of January 21, 2003. For example, an ophthalmic formulation of ketorolac tromethamine 0.5% (Acular® Ophthalmic Solution, Allergan) was approved in the United States for the treatment of seasonal allergic conjunctivitis prior to 2003. (EX1018, 2:1). Acular® Ophthalmic Solution contained BAC as the preservative. (EX1031, 4-5). Furthermore, an ophthalmic solution of diclofenac 0.1% (Voltaren® Ophthalmic Solution, Ciba Ophthalmics. Now marketed by Alcon, a division of Novartis Pharmaceuticals Corp.) was also approved by the FDA prior to 2003 for minimizing postoperative inflammation after cataract surgery. (EX1018, 2:1; EX1027).

151. Moreover, Ogawa described stable aqueous liquid ophthalmic preparations of bromfenac and BAC. (EX1004, 8:4-20, Table 8). In addition, a

stable aqueous liquid ophthalmic preparation of bromfenac was already commercially available in Japan (Bronuck®). (EX1007, 4-6). Additionally, Yanni prepared bromfenac derivatives that were devoid of free carboxyl groups but effective in inhibiting plasma protein influx into the anterior chamber and aqueous humor prostaglandin accumulation. (EX1028, 14:36-39). And Fu solved the stability problems of ophthalmic NSAID- and BAC-containing preparations by adding ethoxylated octylphenols to the formulations. (EX1011, 20:10-21:27).

152. In sum, there was no long-felt, unmet need for an aqueous liquid preparation of an NSAID formulated with BAC for ophthalmic administration by 2003, as researchers in the field had a number of solutions for formulating such stable aqueous ophthalmic preparations. As such, Senju did not meet a long-felt but unmet need for such preparations.

X. The claimed bromfenac preparations were not met with skepticism

153. Senju is unlikely to demonstrate that the claimed aqueous liquid preparations of bromfenac were met with skepticism in January 21, 2003. First, by January 21, 2003, an aqueous ophthalmic formulation of bromfenac was launched in Japan. (EX1029). This formulation contained benzalkonium chloride as a preservative and polysorbate 80 as the surfactant. (EX1029; EX1007, 4). Thus, researches in the relevant field were not skeptical about formulating bromfenac aqueous solutions for ophthalmic use.

154. Nor was there any skepticism regarding formulating similar NSAIDs with BAC as of January 2003. For instance, ketorolac tromethamine (Acular® Ophthalmic Solution, Allergan) contained BAC as the preservative. (EX1031, 4-5). Thus, there was no skepticism in the relevant field that NSAIDs could be formulated with BAC in aqueous ophthalmic preparations. And there was no skepticism in the relevant field regarding making aqueous preparations of bromfenac formulated for ophthalmic use without BAC, as disclosed in Ogawa (Example 5). (EX1004, 9:60-10:3). Therefore, Senju's potential assertion of skepticism by others in the field must fail.

XI. The claimed bromfenac ophthalmic formulations have not received any praises

155. Senju may argue that the claimed ophthalmic formulation of bromfenac received accolades or praise. I am not aware of any praise for the claimed preparations of the '813 patent by experts in the field. Further, because the '813 patent has not received any special recognition or acceptance from the ophthalmic formulation industry, Senju cannot demonstrate that any license to B&L suggests nonobviousness.

XII. Additional evidence of secondary considerations

156. I am not aware of any other allegations of evidence of secondary considerations made by Senju. And even in view of arguments Senju might assert regarding secondary considerations of nonobviousness, the references discussed in

this declaration would have suggested the claimed invention to a person of ordinary skill in the art.

XIII. Conclusion

157. In conclusion, as explained above, a POSA would have had a reason to combine the discussed prior art as claimed and would have had a reasonable expectation of success in developing the claimed preparations of bromfenac. I have also considered Senju's arguments and potential arguments regarding secondary considerations of non-obviousness. Having considered Senju's arguments, my opinion remains unchanged.

158. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Respectfully Submitted,

A handwritten signature in black ink, appearing to read "Paul A. Laskar", with a stylized flourish at the end.

Dr. Paul A. Laskar

Date: November 2, 2015