

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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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

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*Inter Partes* Review No.: IPR2016-00090

**Petition for *Inter Partes* Review of U.S. Patent No. 8,871,813 Under  
35 U.S.C. §§ 311-319 and 37 C.F.R. §§ 42.1-.80, 42.100-.123**

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### **Petitioner's Exhibit List**

<b><i>InnoPharma Exhibit #</i></b>	<b><i>Description</i></b>
<b>1001</b>	Sawa <i>et al.</i> , U.S. Patent No. 8,871,813, "Aqueous Liquid Preparation Containing 2-Amino-3-(4-Bromobenzoyl) Phenylacetic Acid"
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<b>1003</b>	Declaration of Paul A. Laskar, Ph.D.
<b>1004</b>	Ogawa <i>et al.</i> , U.S. Patent No. 4,910,225, "Locally Administrable Therapeutic Composition for Inflammatory Disease"
<b>1005</b>	Desai <i>et al.</i> , U.S. Patent No. 5,603,929, "Preserved Ophthalmic Drug Compositions Containing Polymeric Quaternary Ammonium Compounds"
<b>1006</b>	Desai, <i>et al.</i> , U.S. Patent No. 5,558,876, "Topical Ophthalmic Acidic Drug Formulations"
<b>1007</b>	Certified English translation of "Bromfenac sodium hydrate" in the <i>Japanese Pharmacopoeia 2001 Edition</i> : 27-29, Yakuji Nippo Limited (2001)
<b>1008</b>	FDA approved "BROMDAY™ (bromfenac ophthalmic solution, .09%) Product Label," U.S. Approval: March 24, 2005, ISTA Pharmaceuticals, Inc.
<b>1009</b>	Sallmann <i>et al.</i> , U.S. Patent No. 6,107,343, "Ophthalmic And Aural Compositions Containing Diclofenac Potassium"
<b>1010</b>	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)
<b>1011</b>	Fu <i>et al.</i> , Australian Patent No. AU-B-22042/88, "Preservative System For Ophthalmic Formulations"
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<b>1013</b>	U.S. Patent Application No. 13/687,242, Office Action of August 1, 2013



<b><i>InnoPharma Exhibit #</i></b>	<b><i>Description</i></b>
<b>1014</b>	U.S. Patent Application No. 10/525,006, Applicant Remarks in support of amendment March 26, 2008
<b>1015</b>	U.S. Patent Application No. 10/525,006, Applicant Remarks in support of amendment, September 6, 2011
<b>1016</b>	<i>The Pharmacopeia of the United States of America</i> , Thirty-Eighth Revision and the National Formulary, Thirty-Third Edition
<b>1017</b>	Kapin, <i>et al.</i> , International Patent No. WO 2002/13804, “Method for Treating Angiogenesis-Related Disorders Using Benzoyl Phenylacetic Acid”
<b>1018</b>	Flach, Allan., “Topical Nonsteroidal Antiinflammatory Drugs for Ophthalmic Uses,” <i>Ophthalmic NSAIDs</i> : 77-83 (1996)
<b>1019</b>	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)
<b>1020</b>	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)
<b>1021</b>	Aviv, H., International Patent No. WO 94/05298, “Submicron Emulsions as Ocular Drug Delivery Vehicles”
<b>1022</b>	Bergamini <i>et al.</i> , U.S. Patent No. 5,597,560, “Diclofenac And Tobramycin Formulations For Ophthalmic And Otis Topical Use”
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<b>1024</b>	Excerpt of Plaintiffs’ Opening Markman Brief filed in <i>Senju Pharm. 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).
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<b>1027</b>	"Voltaren," Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, Appl. No. N020037, U.S. FDA, accessed at <a href="http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?A_ppl_No=020037&amp;TABLE1=OB_Rx">http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?A_ppl_No=020037&amp;TABLE1=OB_Rx</a>
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<b>1029</b>	"ISTA Pharmaceuticals Submits New Drug Application for Xibrom™ QD (once-daily), News Release, ISTA Pharmaceuticals (December 20, 2007)
<b>1030</b>	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)
<b>1031</b>	"Acular®" and "Azopt™," Physician's Desk Reference 54: 486- 487, 491-492 (2000).
<b>1032</b>	Doughty, M., "Medicines Update for optical practitioners- Part 11," <i>Optician</i> 5853 (223), (2002).
<b>1033</b>	Reddy, Indra K., <i>Ocular Therapeutics and Drug Delivery: A Multi-Disciplinary Approach</i> : 42-43, 390 (1996).
<b>1034</b>	Fan, T., "Determination of Benzalkonium Chloride in Ophthalmic Solutions Containing Tyloxapol by Solid-Phase Extraction and Reversed-Phase High-Performance Liquid Chromatography," <i>Journal of Pharmaceutical Sciences</i> 82 (11): 1172-1174, American Pharmaceutical Association, United States (1993).

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<b>1035</b>	Wong, Michelle, International Patent No. WO 94/15597, "Ophthalmic Compositions Comprising Benzyl lauryldimethylammonium Chloride" (filed January 11, 1993; issued July 21, 1994).
<b>1036</b>	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).
<b>1037</b>	FDA approved "ALREXTM (loteprednol etabonate ophthalmic suspension) 0.2% Product Label," U.S. Approval: 1998, Bausch & Lomb Pharmaceuticals.
<b>1038</b>	FDA approved "LOTEMAXTM (loteprednol etabonate ophthalmic suspension) 0.5% Product Label," U.S. Approval: 1998, Bausch & Lomb Pharmaceuticals.
<b>1039</b>	"TOBRADEX®" Physician's Desk Reference 54: 490 (2000).
<b>1040</b>	"Alomide® 0.1%" Physician's Desk Reference 50: 469 (1996).
<b>1041</b>	Johnson, R., <i>et al.</i> , U.S. Patent No. 2,880,130, "Anti-Inflammatory Steroid Solutions".
<b>1042</b>	Johnson, R., <i>et al.</i> , U.S. Patent No. 2,880,138, "Anti-Inflammatory Steroid Solutions".
<b>1043</b>	Kawabata, <i>et al.</i> , Canadian Patent No. CA 2 383 971 A1, "Prophylactic and Therapeutic Medicaments for Ophthalmic Uses".
<b>1044</b>	Patani, G., <i>et al.</i> , "Bioisoterism: A Rational Approach in Drug Design," Chem. Rev. 96: 3147-3176 (1996).
<b>1045</b>	FDA approved "XIBROMTM (bromfenac ophthalmic solution, .09%) Product Label," ISTA Pharmaceuticals, Inc.
<b>1046</b>	Senju Pharmaceutical Co., Ltd. Press Releases, "The approval of BRONUCK® (bromfenac sodium hydrate ophthalmic solution) as an import drug in China," <a href="http://www.senju.co.jp/">http://www.senju.co.jp/</a> , accessed at <a href="http://www.senju.co.jp/english/news/_icsFiles/afieldfile/2009/11/18/2009111814br.pdf">http://www.senju.co.jp/english/news/_icsFiles/afieldfile/2009/11/18/2009111814br.pdf</a> , published November 17, 2009, 1 page.

<b><i>InnoPharma Exhibit #</i></b>	<b><i>Description</i></b>
<b>1047</b>	FDA approved "PROLENSATM (bromfenac ophthalmic solution, 0.07%) Product Label," U.S. Approval: April 5, 2013, Bausch & Lomb Incorporated
<b>1048</b>	"Borax (Sodium tetraborate)," Biochemicals and Reagents: 175, Sigma-Aldrich (2000-2001).
<b>1049</b>	Ali, <i>et al.</i> , U.S. Patent No. 6,071,904, "Process for Manufacturing Ophthalmic Suspensions".
<b>1050</b>	Story, M., <i>et al.</i> , European Patent No. 0274870, "Micelles containing a non-steroidal antiinflammatory compound" (filed December 12, 1987; issued July 7, 1988)
<b>1051</b>	"DuractTM," Physician's Desk Reference 52:3035-3037 (1998).
<b>1052</b>	Curriculum Vitae of Paul A. Laskar, Ph.D.
<b>1053</b>	U.S. Patent Application No. 10/525,006, Applicant Remarks in support of amendment Oct. 25, 2010

## I. INTRODUCTION

InnoPharma Licensing, Inc., InnoPharma Licensing LLC, InnoPharma Inc., InnoPharma LLC, Mylan Pharmaceuticals Inc., and Mylan Inc. (collectively, “Petitioner”) petition for *Inter Partes* Review, seeking cancellation of claims 1-27 (“challenged claims”) of U.S. Patent No. 8,871,813 (“the ’813 patent”) (EX1001), owned by Senju Pharmaceutical Co., Ltd. (“Patent Owner”).

## II. OVERVIEW

The Board has already issued its Decision Instituting *Inter Partes* Review (“Decision”) on all challenged claims of the ’813 patent based on the Ogawa/Sallmann prior art. *Lupin Ltd. v. Senju Pharm. Co., Ltd.*, IPR2015-01105 [Paper No. 9, p. 15]. In its Decision, the Board found that Petitioner Lupin Ltd. and Lupin Pharmaceuticals Inc. (collectively “Lupin”) had demonstrated a reasonable likelihood that claims 1-27 of the ’813 patent are obvious. *Id.* The Board instituted IPR of the challenged claims on the ground that claims 1-27 are reasonably likely to be obvious over Ogawa and Sallmann. *Id.* at pg. 16. Petitioner hereby files its own petition that raises obviousness in view of Ogawa and Sallmann and concurrently seeks to join the instituted IPR proceedings.

The challenged claims of the ’813 patent are primarily directed to an aqueous formulation of *bromfenac* (a non-steroidal anti-inflammatory drug (“NSAID”)) with *tyloxapol* (a non-ionic surfactant) with the inclusion of other components such as

boric acid, sodium tetraborate, and water. At the relevant time, tyloxapol was a known non-ionic surfactant in aqueous formulations of NSAIDs while bromfenac was a known NSAID previously formulated with another non-ionic surfactant, polysorbate 80. Thus, the purported inventors of the aqueous preparations of the challenged claims did nothing more than switch polysorbate 80 for tyloxapol (both well-known non-ionic surfactants). Swapping known alternatives from the prior art, according to their known functions to achieve predictable results, is not innovation. *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007).

### **III. STANDING (37 C.F.R. § 42.104(a); PROCEDURAL STATEMENTS)**

Petitioner certifies that (1) the '813 patent is available for IPR; and (2) Petitioner is not barred or estopped from requesting IPR of any claim of the '813 patent on the grounds identified herein. This Petition is filed in accordance with 37 C.F.R. § 42.106(a). Filed herewith are a Power of Attorney and an Exhibit List pursuant to § 42.10(b) and § 42.63(e). The required fee is paid through online credit card, and the Office is authorized to charge any fee deficiencies and credit overpayments to Deposit Acct. No. 160605 (Customer ID No. 00826).

### **IV. MANDATORY NOTICES (37 C.F.R. § 42.8(a)(1))**

#### **A. Each Real Party-In-Interest (37 C.F.R. § 42.8(b)(1))**

The real parties in interest for this petition are InnoPharma Licensing Inc., InnoPharma Licensing LLC, InnoPharma Inc., InnoPharma LLC, Mylan Pharmaceuticals Inc., and Mylan Inc.

**B. Notice of Related Matters (37 C.F.R. § 42.8(b)(2))**

**1. Judicial Matters**

The '813 patent is currently the subject of the following litigations: *Senju Pharm. Co., Ltd. et al. v. InnoPharma Licensing, Inc. et al.*, C.A. 1:15-cv-03240 (D.N.J.); *Senju Pharm. Co., Ltd., et al. v. Lupin, Ltd. et al.*, C.A. No. 1:15-cv-00335 (D.N.J.); *Senju Pharm. Co., Ltd., et al. v. Apotex, Inc., et al.*, C.A. No. 1:15-cv-00336 (D.N.J.); *Senju Pharm. Co., Ltd., et al v. InnoPharma Licensing, Inc. et al.*, C.A. No. 1:14-cv-06893 (D.N.J.); *Senju Pharm. Co., Ltd., et al v. Paddock Labs., LLC et al.*, C.A. No. 1:15-cv-00087-SLR (D. Del.); *Senju Pharma. Co., Ltd., et al v. Paddock Labs., LLC et al.*, C.A. No. 1:15-cv-00337 (D.N.J.); *Senju Pharm. Co., Ltd., et al v. Metrics, Inc.*, C.A. No. 1:14-cv-03962 (D.N.J.); and *Senju Pharm. Co., Ltd., et al v. Watson Labs., Inc.*, C.A. No. 1:15-cv-05591 (D.N.J.).

**2. Administrative Matters**

U.S. Patent No. 8,871,813 (“the ’813 patent”) is the subject of a petition for *inter partes* reviews (IPR2015-01105) filed by Lupin Ltd. and Lupin Pharmaceuticals (collectively “Lupin”) on April 23, 2015, which was instituted on October 27, 2015 as to claims 1-27. Petitioner seeks joinder with that IPR, for the

reasons expressed in the concurrently filed Motion for Joinder under 35 U.S.C. § 315(c), 37 C.F.R. §§ 42.22 and 42.122(b).

Petitioner is also aware of at least the following related family members: application No. 14/483,903 (“the ’903 application”), now U.S. Patent No. 8,927,606 (“the ’606 patent”), which is a division of application No. 14/261,720 (“the ’720 application”), now the ’813 patent, which is a division of application No. 14/165,976 (“the ’976 application”), now U.S. Patent No. 8,754,131 (“the ’131 patent”), which is a division of application No. 13/687,242 application (“the ’242 application”), now U.S. Patent No. 8,669,290 (“the ’290 patent”), which is a division of application No. 13/353,653 (“the ’653 application”), now U.S. Pat. No. 8,497,304 (“the ’304 patent”), which is a division of application No. 10/525,006 (“the ’006 application”), now U.S. Patent No. 8,129,431 (“the ’431 patent”), which was the U.S. National Stage of PCT Application No. PCT/JP2004/000350 (“the ’350 application”), which claimed priority to Japanese Application No. 2003-12427. Related family member applications U.S. Application Serial Nos. 14/269,692 and 14/502,014 are currently pending before the Patent Office.

U.S. Patent No. 8,669,290 (“the ’290 patent”) is the subject of the following *inter partes* reviews: IPR2014-01043 filed by Metrics Inc., which was settled on July 8, 2015; IPR2015-00902 filed by Petitioner on March 19, 2015, which was



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instituted on August 7, 2015 as to claims 1-30; IPR2015-01099 filed by Lupin on April 23, 2015, which was instituted on October 27, 2015 as to claims 1-30.

U.S. Patent No. 8,129,431 (“the ’431 patent”) is the subject of the following *inter partes* reviews: IPR2014-01041 filed by Metrics Inc., which was settled on July 8, 2015; IPR2015-00903 filed by Petitioner on March 19, 2015, which was instituted on August 7, 2015 as to claims 1-22; IPR2015-01871 filed by Lupin on September 4, 2014.

U.S. Patent No. 8,754,131 (“the ’131 patent”) is the subject of a petition for *inter partes* reviews (IPR2015-01097) filed by Lupin on April 23, 2015, which was instituted on October 27, 2015 as to claims 1-30.

U.S. Patent No. 8,927,606 (“the ’606 patent”) is the subject of a petition for *inter partes* reviews (IPR2015-01100) filed by Lupin on April 23, 2015, which was instituted on October 27, 2015 as to claims 1-30.

Petitioners have filed concurrently with this Petition, Petitions for *inter partes* review of the following U.S. Patents related to the ’813 patent: U.S. Patent Nos. 8,754,131 and 8,927,606.

**C. Designation of Lead and Back-Up Counsel and Service (37 C.F.R. §§ 42.8(b)(3), 42.8(b)(4), 42.10(a), and 42.10(b)):**

Lead Counsel: Jitendra Malik, Ph.D. (Registration No. 55,823; jitty.malik@alston.com). Backup Counsel: Hidetada James Abe (Registration No.

61,182; james.abe@alston.com); Lance Soderstrom (Registration No. 65,405; lance.soderstrom@alston.com). Please direct all correspondence to lead counsel at: 4721 Emperor Boulevard, Suite 400, Durham, North Carolina 27730. Petitioner consents to email service. Telephone: (919) 862-2200. Facsimile: (919) 862-2260.

**V. STATEMENT OF THE PRECISE RELIEF REQUESTED AND THE REASONS THEREFORE (37 C.F.R. § 42.22(a))**

Petitioners request IPR and cancellation of claims 1-27. Petitioners' full statement of the reasons for the relief requested is set forth in detail below.

**VI. THE '813 PATENT**

The challenged claims of the '813 patent are directed to a stable aqueous liquid preparation. The '813 patent has three independent claims (claims 1, 7, and 13). Independent claim 1 is directed to a stable aqueous liquid preparation consisting essentially of: (a) about 0.05 w/v % to about 0.2 w/v % of 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof; (b) tyloxapol in an amount sufficient to stabilize component (a); (c) boric acid; (d) sodium tetraborate; and (e) water; ; and wherein said stable liquid preparation is formulated for ophthalmic administration. (EX1001, 11:30-42).<sup>1</sup>

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<sup>1</sup> Citations are as follows: X:YY-ZZ (col:lines; patent); X:Y:Z (page:col:para; journal article); X:Y (page:para; journal article).

Independent claim 7 is similar to claim 1, but the principal difference is that it recites a stability: “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, 12:9-12).

Independent claim 13 is similar to claim 1, but is different in that it affirmatively excludes mannitol. (EX1001, 12:50-51).

#### **A. Claim Construction**

Petitioner believes that no terms or phrases require specific construction for the purpose of this IPR. Indeed, the Board recently determined that “express construction of any claim term is not necessary” for the purposes of rendering a decision to institute review of the ’813 patent. *Lupin Ltd., v. Senju Pharm. Co., Ltd.*, IPR2015-01105 [Paper No. 9, pg. 7]. Therefore, in accordance with 37 C.F.R. § 42.100(b), the challenged claims must be given their broadest reasonable interpretation in light of the specification of the ’813 patent.

#### **VII. PERSON OF SKILL IN THE ART (“POSA”) & STATE OF THE ART**

A POSA would have had education and/or experience in the field of ophthalmic formulations and drug delivery, and knowledge of the scientific literature concerning the same, specifically pharmaceutical formulations for ophthalmic administration, including those comprising anti-inflammatory compounds (such as NSAIDs) 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 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. (EX1003, ¶ 20).

As of January 21, 2003, the state of the art pertinent to the '813 patent was such that aqueous liquid preparations containing NSAIDs (including bromfenac) and tyloxapol were disclosed, and well known. For example, Desai disclosed a formulation that included bromfenac and tyloxapol, and benzalkonium chloride ("BAC"), in addition to other ingredients. (EX1005, Abstract; 2:18-23, 3:30-45, 6:13-16, 6:25-28; EX1017, 4:1-23, 6:8-9, 8:13-22, Formulation 3; EX1003, ¶¶ 31, 39). It was also known that NSAID compounds were suitable and desirable for ophthalmic administration (EX1018, 1:1; EX1003, ¶¶ 25-26), and that the NSAID bromfenac was specifically described in ophthalmic formulations in the prior art. (EX1002, 2:1:2; EX1003, ¶¶ 29-31, 76). Likewise, ethoxylated octylphenol surfactants, including tyloxapol, have been used to stabilize NSAIDs in ophthalmic preparations for at least a half-century and were described in combination with the NSAIDs diclofenac and ketorolac (together with BAC) more than a year before the effective filing date. (EX1010, 3:1; EX1003, ¶¶ 32-37). BAC was widely used—

indeed one of the *most* widely used—preservative excipients in ophthalmic formulations. (EX1030, 2:1:1; EX1003, ¶ 32-33).

It was also well-known that NSAIDs bearing acidic groups such as a carboxyl group (like bromfenac, diclofenac, ketorolac, and others) could be incompatible with quaternary ammonium compounds such as BAC in ophthalmic formulations, because they could form a complex with the quaternary ammonium compounds. (EX1006, 1:10-24; EX1005, 1:27-34; EX1022, 2:18-24; EX1035, 4:1-5; EX1003, ¶ 33). Indeed, bromfenac and diclofenac are considered acidic NSAID drugs. (EX1053, 1; EX1003, ¶ 41, n. 10). Moreover, the prior art taught that these complexes could result in precipitate formation, adversely affecting the preservative activity of BAC and reducing the activity of the acidic NSAID. (EX1035, 4:11-17; EX1011, 5:1-7; EX1003, ¶ 33). Indeed, even the patentee has admitted as much. (EX1001, 1:57-62; EX1003, ¶ 41, n. 10).<sup>2</sup>

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<sup>2</sup> As the patentee explained “[b]enzalkonium chloride is a widely used preservative in ophthalmic solutions. However, benzalkonium chloride and other quaternary ammonium compounds are generally considered to be incompatible with ophthalmic compositions of drugs with acidic groups, such as nonsteroidal anti-inflammatory drugs. These preservatives lose their ability to function as they form complexes with the charged drug compounds.” (EX1001, 1:57-62).

The prior art also described stable ophthalmic formulations of acidic NSAIDs containing an ethoxylated octylphenol surfactant like tyloxapol. (EX1004, 3:48-53, 10:5-18; EX1011, 12:1-11; EX1003, ¶¶ 34-37, 39). As of 2003, ethoxylated octylphenol surfactants were thought to either: (1) prevent the complexes from forming (EX1033, 5); or (2) solubilize the formed complexes so that they stayed in solution. (EX1050, 4:19-20; EX1003, ¶¶ 35, 143, n. 23).

### **VIII. IDENTIFICATION OF CHALLENGE (37 C.F.R. § 42.104(b))**

IPR of claims 1-27 of the '813 patent is respectfully requested on the specific grounds of unpatentability outlined below. Per 37 C.F.R. § 42.6(d), copies of the references are filed herewith. In support of the proposed grounds, this Petition includes the declaration of a technical expert, Paul A. Laskar, Ph.D. (EX1003), explaining what the art would have conveyed to a POSA as of January 21, 2003. Dr. Laskar is an expert in the field of ophthalmic formulations.

<b>Ground</b>	<b>References</b>	<b>Basis</b>	<b>Claims Challenged</b>
1	Ogawa in light of Sallmann	103	1-27
2	Ogawa in light of Sallmann and Fu	103	1-27
3	Ogawa in light of Sallmann and Yasueda	103	1-27

Prior art references in addition to the primary references listed above provide further background in the art, further motivation to combine the teachings of these references and/or further support for why a person of skill in the art would have a

reasonable expectation of success in combining the teachings of the references to arrive at the methods recited in the challenged claims.

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

**1. Aqueous Ophthalmic Preparation of Bromfenac**

As of the priority date of the '813 patent, bromfenac, diclofenac, and ketorolac were well-known NSAIDs useful for treating inflammation in the eye. (EX1002, 2:1:2; EX1003, ¶¶ 25-31). These compounds each possessed a carboxylic acid group ( $\text{—COOH}$ ). By January 21, 2003, bromfenac had been formulated with non-ionic surfactants, including but not limited to tyloxapol and polysorbate 80, in aqueous preparations for ophthalmic delivery. The Ogawa patent (EX1004) described (and exemplified) an aqueous ophthalmic formulation containing: (1) bromfenac and (2) polysorbate 80. (EX1004, 9:5-10:19). Similarly, U.S. Patent No. 5,603,929 to Desai *et al.* (“the Desai '929 patent”) described a storage-stable ophthalmic formulation containing bromfenac, and optionally any one of a number of conventional surfactants, including tyloxapol. (EX1005, 3:38-41; Hara (EX1002); U.S. Patent No. 5,558,876 to Desai *et al.* (EX1006); BRONUCK, Japanese Pharmacopeia (EX1007); and BROMDAY Prescribing Information (EX1008)).

**2. Tyloxapol and Related Surfactants in NSAID Aqueous Ophthalmic Preparations**

By January 21, 2003, tyloxapol and related alkylaryl polyether surfactants were well-known non-ionic surfactants used in prior art formulations containing

NSAIDs. For example, the Sallmann patent (EX1009) described liquid ophthalmic formulations containing: (1) diclofenac sodium (an NSAID) and (2) tyloxapol (a surfactant). (EX1009, 2:6-8, 4:52-62). The Desai '929 patent described a storage-stable ophthalmic formulation containing bromfenac, and optionally any one of a number of conventional surfactants, including tyloxapol. (EX1005, 3:38-41).

Tyloxapol, like polysorbate 80, was successfully used to stabilize aqueous ophthalmic formulations as early as the 1960s. (EX1009, 4:62; EX1010, 4:2:2-4:2:4; EX1003, ¶¶ 34, 36-41). Notably, the prior art disclosed: (1) that tyloxapol was effective in stabilizing NSAIDs (EX1003, ¶ 36; EX1011); (2) examples where tyloxapol was a preferred non-ionic surfactant for use in ophthalmic formulations containing acidic NSAIDs (EX1009, 4:62; EX1003, ¶¶ 36, 41, 72); and (3) that tyloxapol was superior to polysorbate 80 as a surfactant in aqueous liquid formulations of an acidic compound. (EX1012, 7:20-43). In fact, in the prior art, only a finite number of non-ionic surfactants, including tyloxapol and polysorbate 80, had been used in approved ophthalmic formulations. (EX1012, 4:61-64; EX1009, 4:52-62).

**B. Ground 1: Claims 1-27 Are Unpatentable Under 35 U.S.C. § 103(a) over Ogawa in light of Sallmann**

For Ground 1, Petitioner relies on the teachings of **Ogawa** (EX1004) in light of **Sallmann** (EX1009). Both references disclose a prior art ophthalmic formulation



of an NSAID and a non-ionic surfactant, similar to what is claimed in the '813 patent. The challenged claims differ from prior art aqueous liquid ophthalmic formulations of an NSAID *primarily* in the substitution of one well-known non-ionic surfactant (tyloxapol) for another well-known non-ionic surfactant (polysorbate 80). When viewed against the prior art, it is clear that the alleged inventors of the '813 patent did nothing more than swap one well-known component from a prior art formulation with another known component to be used for the same purpose. *Sundance, Inc. v. DeMonte Fabricating Ltd.*, 550 F.3d 1356, 1366-67 (Fed Cir. 2008) (explaining that rearranging old elements performing the same function yielding no more than one would expect is obvious). Petitioner will address the independent claims first, and then address the dependent claims.

**1. Ogawa (EX1004) and Sallmann (EX1009)**

U.S. Patent No. 4,910,225 (“Ogawa”) (EX1004) issued March 20, 1990 (§ 102(b) prior art). Ogawa was cited in the prosecution history of the '813 patent and referenced in the Background Art section of the '813 patent. (EX1001, 1:46-47). Ogawa, however, was not relied upon in rejecting any claims pending during prosecution.<sup>3</sup> Ogawa describes a specific example (Example 6) of an aqueous preparation comprising the sodium salt of bromfenac (sodium 3-(4-bromobenzoyl)-

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<sup>3</sup> Ogawa was relied upon during prosecution of the '290 patent. (EX1013, 7:5-14).

2-aminophenylacetate monohydrate) and the non-ionic surfactant polysorbate 80. Ogawa further describes that the formulation of Example 6 maintains greater than 92% of the original amount of bromfenac after storage at 60°C for 4 weeks. (EX1004, 10:49-51, 14:45-50).

**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). The closeness of the disclosed formulations between the '813 patent and Ogawa can be seen in a comparison of the components shown below.

<b>Component</b>	<b>'813 Patent Example 2 (EX1001, 10:35-51)</b>	<b>Ogawa Example 6 (EX1004, 10:5-18)</b>
Bromfenac sodium	0.1 g (3/2 hydrate)	0.1 g (monohydrate)
Boric acid	1.1 g	1.25 g
Borax	1.1 g	1.0 g
BAC	0.005 g	0.005 g
<i>Surfactant</i>	<i>0.05 g (tyloxapol)</i>	<i>0.15 g (polysorbate 80)</i>
PVP	2.0 g	2.0 g
Sodium edetate	0.02 g	0.02 g (disodium)
Sodium hydroxide	q.s.	"The pH adjustment is generally conducted with sodium hydroxide . . . ." 3:62-64.
Water	To make 100 mL	To make 100 mL
pH	8.16	8
<i>Sodium sulfite</i>		<i>0.2 g</i>

U.S. Patent No. 6,107,343 (“Sallmann”) (EX1009) issued August 22, 2000 (§ 102(b) prior art). Sallmann was cited in the prosecution history of the ’813 patent, but not relied upon in rejecting any claims during prosecution. Sallmann describes a specific example (Example 2) of an aqueous preparation comprising diclofenac potassium 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).

Bromfenac and diclofenac are both acidic NSAIDs sharing common structural features, most notably a phenylacetic acid moiety (phenyl-CH<sub>2</sub>-COOH). (EX1003, ¶¶ 26, 29). Indeed, in this regard, the Board has observed that “bromfenac and diclofenac were known to share several structural features” in related proceedings. *InnoPharma Licensing Inc., et al. v. Senju Pharm. Co., Ltd.*, IPR2015-00902 [Paper No. 17, p. 12].

**2. Independent Claims 1, 7, and 13**

**a. Claim 1**

Claim 1 would have been obvious to a POSA reading Ogawa in view of Sallmann for the reasons explained below. (EX1003, ¶ 52).

'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, 14:45-50).
(a) a first component; (b) a second component;	See below.
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-aminophenyl-acetate (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-aminophenyl-acetate(bromfenac) <b>monohydrate</b> . (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-aminophenyl-acetate (bromfenac) monohydrate as the only pharmaceutical active ingredient

<b>'813 patent claim 1</b>	<b>Disclosure in Ogawa (EX1004) and Sallmann (EX1009)</b>
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 of sodium 3-(4-bromobenzoyl)-2-aminophenyl-acetate (bromfenac) monohydrate for 100 ml of the ophthalmic solution, which is 0.1 w/v %. (EX1004, 4:42-46, 10:8-9).
the second component is tyloxapol	Sallmann Example 2 contains tyloxapol (EX1009, 8:1-10).
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). Sallmann Example 2 contains 1.0 mg/ml of tyloxapol, which is 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, 14:45-50).</p>
wherein said stable liquid preparation is formulated for ophthalmic administration.	<p>Ogawa: “An ophthalmic composition according to the invention can treat effectively inflammatory eye disease ...” (EX1004, Abstract). (EX1004, 2:47-50, 3:31-33).</p> <p>Sallmann: “The present invention relates to an ophthalmic composition for treating</p>

'813 patent claim 1	Disclosure in Ogawa (EX1004) and Sallmann (EX1009)
	inflammatory ocular conditions, for treating glaucoma...which composition comprises a therapeutically effective amount of diclofenac potassium and a carrier.” (EX1009, 1:60-65). (EX1009, 3:20-24).

The components in Ogawa Example 6, with the substitution of the surfactant according to Sallmann Example 2, meets the requirement of claim 1 that the “stable aqueous liquid preparation consist[] essentially of” the claimed components. By using the phrase “consisting essentially of,” Claim 1 allows for “unlisted ingredients that do not materially affect the basic and novel properties of the invention.” *Ecolab, Inc. v. FMC Corp.*, 569 F.3d 1335, 1343 (Fed. Cir. 2009). The claims of the '813 patent recite that the formulation of claim 1 may additionally contain one or more additives selected from the group consisting of a buffer, thickener, stabilizer, chelating agent, and pH controlling agent. (EX1001, claim 27). Therefore, the term “consisting essentially of” does not exclude buffers, thickeners, stabilizers, chelating agents, or pH controlling agents.<sup>4</sup>

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<sup>4</sup> Further, claim 24 depends on claim 1 and recites that the claimed formulations do not include any preservative, which in accordance with the doctrine of claim differentiation suggests that claim 1 does not exclude the additional of a

The components that are present in Ogawa Example 6 that are not present in claim 1 are disodium edetate, BAC, PVP, and sodium sulfite. The disclosure of the '813 patent, however, shows that these additives will not materially affect the alleged basic and novel properties of the invention that “the [claimed] aqueous solution becomes stable within a pH range giving no irritation to eyes, and change of the 2-amino-3-(4-bromobenzoyl)phenyl acetic acid over time can be inhibited, and . . . deterioration in the preservative effect of said preservative can be inhibited for a long period of time.” (EX1001, 2:34-47, Abstract; EX1003, ¶ 62). The '813 patent specification expressly allows for many other ingredients to be present in the formulation, including chelating agents such as sodium edetate, thickeners such as PVP, preservative such as BAC, and stabilizers such as sodium sulfite. (EX1001, 2:33-35, 2: 37-43, 5:43-56). As suggested by the '813 patent itself as well as Ogawa, the presence of these additives would not adversely affect the alleged basic and novel properties of the claimed invention. (EX1003, ¶ 66).

- (i) **It would have been obvious to substitute tyloxapol from Sallmann’s Example 2 for polysorbate 80 in Ogawa’s Example 6**

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preservative. Otherwise, claim 24 would be superfluous. *Tandon Corp. v. United States Int’l Trade Comm’n*, 831 F.2d 1017, 1023 (Fed. Cir. 1987).

A POSA would have had reason to modify Ogawa in view of the teachings in Sallmann to arrive at the formulation recited in claim 1. (EX1003, ¶ 49). Both Ogawa and Sallmann relate to ophthalmic formulations of structurally-similar acidic NSAIDs containing a non-ionic surfactant, and are within the pertinent art to the claims of the '813 patent. (EX1003, ¶ 71.). As shown in the claim chart above, the *primary* difference between the stable aqueous preparation of Ogawa's Example 6 and claim 1 is that Ogawa's Example 6 includes polysorbate 80 as the non-ionic surfactant, whereas claim 1 recites tyloxapol, another known non-ionic surfactant. Sallmann's Example 2 provides the non-ionic surfactant tyloxapol in an aqueous liquid ophthalmic formulation of another NSAID (diclofenac potassium).

Prior to January 21, 2003, the prior art described ophthalmic formulations of acidic NSAIDs containing a non-ionic surfactant like tyloxapol. (EX1004, 3:48-53, 10:5-18; EX1011, 12:1-8; EX1019, 1:1:2; EX1020, 1:2:1, 2:Scheme 1; EX1017, 4:1-23, 6:8-9, 8:13-22, Formulation 3; EX1009, 8:1-15; EX1003, ¶¶ 36, 38-39). Moreover, Sallmann teaches that tyloxapol may be a better surfactant than polysorbate 80. Specifically, Sallmann teaches that tyloxapol (another non-ionic surfactant) was the preferred surfactant for use in aqueous ophthalmic preparations of diclofenac (another acidic NSAID). (EX1009, 4:62). Indeed, looking to the state of the art, a POSA would have known that substituting polysorbate 80 with tyloxapol would successfully, and predictably, result in a stable formulation of bromfenac



because they had previously been used interchangeably as surfactants in ophthalmic formulations. (EX1021, 13:8-10; EX1022, 4:24-31; EX1003, ¶ 40). The Board has observed that Desai discloses that polysorbates and/or tyloxapol may be used as surfactants in ophthalmic solutions containing be diclofenac or bromfenac. *Lupin Ltd. v. Senju Pharm. Co., Ltd.*, IPR2015-01097 [Paper No. 9, pp. 11].

Ogawa teaches that the aqueous liquid bromfenac preparations formulated with polysorbate 80 is stable and will be useful for ophthalmic administration. (EX1004, 10:5-18, 10:50-52 and 14:45-50; EX1003, ¶¶ 50, 63). And Sallmann teaches that tyloxapol is a preferred solubilizer. (EX1009, 4:62; EX1003, ¶ 72). *Sinclair & Carroll Co., v. Interchemical Corp.*, 325 U.S. 327, 334 (1945).

In addition to being a better surfactant, as discussed above with respect to the background art which is incorporated by reference, it was also known that tyloxapol was a better solubilizer than polysorbate 80 for acidic compounds in aqueous ophthalmic formulations. (EX1012, Table 4, 5; EX1003, ¶¶ 73-75, n. 13). A POSA would have had a reasonable expectation of success substituting tyloxapol for polysorbate 80 because Ogawa provides working examples of bromfenac preparations formulated with polysorbate 80, and a POSA would have understood from the state of the art that tyloxapol is superior to polysorbate 80 in solubilizing another acidic ophthalmic drug. (EX1004, 10:5-18; EX1012, Table 4, 5; EX1003, ¶¶ 73-75, n. 13). The prior art disclosed multiple stable aqueous preparations of

acidic NSAIDs formulated with tyloxapol (and other closely related non-ionic surfactants). (EX1009, 8:1-15; EX1011, 18:5-28, Example 2, 5; EX1003, ¶¶ 38-39).

Accordingly, a POSA would have had a reasonable expectation of success in substituting tyloxapol for polysorbate 80 because the prior art included multiple examples of stable aqueous preparations containing NSAIDs (similar to bromfenac) formulated with tyloxapol (and other closely related non-ionic surfactants). (EX1009, 8:1-15; EX1011, 18:5-28, Example 2, 5; EX1003, ¶¶ 39-41, 71-72, 74-75). The Board has observed in instituting IPR of the '813 patent that “tyloxapol and polysorbate 80 are nonionic surfactants that were known to be used interchangeably in ophthalmic formulations,” that a POSA “would have been motivated to substitute tyloxapol for the polysorbate 80 included Ogawa’s formulation,” and that the tyloxapol concentration in Sallmann address the requirement that the amount of tyloxapol is sufficient to stabilize. *Lupin Ltd. v. Senju Pharm. Co., Ltd.*, IPR2015-01105 [Paper No. 9, p. 9-11]; *see also InnoPharma Licensing, Inc. v. Senju Pharm. Co., Ltd.*, IPR2015-00902 [Paper No. 17, p. 11].

In addition, a POSA would have found it obvious to try to prepare a bromfenac ophthalmic formulation containing tyloxapol as the surfactant because tyloxapol was one of three preferred surfactants—*i.e.*, there was a finite number of predictable solutions known—used to stabilize a similar NSAID (diclofenac). (EX1009, 4:56-62; EX1003, ¶ 72-73). *Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC*, 683 F.3d

1356, 1364-65 (Fed Cir. 2012). The law is clear that “[W]hen a patent ‘simply arranges old elements with each performing the same function it had been known to perform’ and yields no more than one would expect from such an arrangement, the combination is obvious.” *KSR*, 550 U.S. at 416 (citing *Sakraida v. AG Pro, Inc.*, 425 U.S. 273 (1976)).

**(ii) Sallmann teaches that the amount of tyloxapol is sufficient to stabilize the bromfenac, or in the alternative it would have been obvious to do so according to the teachings of Sallmann and Ogawa**

Claim 1 of the '813 patent requires that “the second component is tyloxapol and is present in said liquid preparation in an amount *sufficient to stabilize* said first component.” (EX1001, 11:40-42). Sallmann states “[a]nother preferred solublizer 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) (emphasis added). An amount of tyloxapol sufficient to solubilize the active ingredient should also be an amount sufficient to stabilize the active ingredient. (EX1003, ¶¶ 72, 74-75, 91). Accordingly, Sallmann explicitly teaches this limitation.

Further, Sallmann Example 2 contains 1.0 mg/ml of tyloxapol, which is 0.1% according to a correlation of the mg/ml of diclofenac potassium to the indicated percentage. (EX1009, 8:1-10). The '813 patent, on the other hand,

discloses a tyloxapol concentration range between 0.01 w/v % and 0.5% w/v, and preferably between 0.02 w/v % and 0.05 w/v %. (EX1001, 5:20-25). Accordingly, the tyloxapol concentration disclosed in Sallmann Example 2, although above the preferred maximum disclosed in the '813 patent, is still well within the general range disclosed and, thus, is an amount sufficient to stabilize the bromfenac. (EX1003, ¶ 63). The Board has also observed in related proceedings that “Sallmann adds tyloxapol to an NSAID-BAC preparation in an amount that falls within the preferred amount disclosed in the '290 patent.” *InnoPharma Licensing, Inc. v. Senju Pharm. Co., Ltd.*, IPR2015-00902 [Paper No. 17, p. 8]; *Lupin Ltd. v. Senju Pharm. Co., Ltd.*, IPR2015-01105 [Paper No. 9, p. 11]. Overlapping ranges establish a *prima facie* case of obviousness. *In re Peterson*, 315 F.3d, 1325, 1329-30 (Fed. Cir. 2003); *In re Woodruff*, 919 F.2d 1575, 1578 (Fed. Cir. 1990).

Further the requirement that the “amount [be] sufficient to stabilize” the bromfenac is met by Ogawa. (EX1004, 10:50-52, 14:45-50; EX1003, ¶ 63). Ogawa’s Example 6 was tested under conditions of 60°C for 4 weeks and, as shown in Table 11 of Ogawa, more than 90% of the original bromfenac in the preparation remained after 4 weeks. (EX1004, 10:50-52, 14:45-50). Tyloxapol is more superior to polysorbate 80 as a stabilizer; thus, the substitution of tyloxapol should increase the stability level. (EX1011, 18:5-28, Example 2, 5; EX1003, ¶¶ 41, 63, 75, 85,

106). Accordingly, the remaining bromfenac would increase if tyloxapol were used as suggested by Sallmann, instead of polysorbate 80.

In the alternative, a POSA would have found it obvious to adjust the amount of tyloxapol in the formulation so that it was sufficient to stabilize the bromfenac. (EX1003, ¶ 63). In Sallmann, the concentration of tyloxapol “depends especially on the concentration of the active ingredient. The amount added is typically sufficient to solubilize the active ingredient. For example, the concentration of the solubilizer is from 0.1 to 5000 times the concentration of the active ingredient.” (EX1009, 4:63-67). Accordingly, a POSA would have been motivated to include a sufficient amount of tyloxapol to stabilize the bromfenac as suggested by Sallmann. (EX1003, ¶ 63). *See In re Aller*, 220 F.2d 454, 458 (C.C.P.A. 1955); *Peterson*, 315 F.3d at 1330.

Furthermore, the degree of stability represents a “latent” property of an otherwise obvious preparation—a preparation suggested by Ogawa and Sallmann—and the inventors’ mere recognition of that property does not render nonobvious the modified preparation of Ogawa in view of Sallmann. *In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991) (“Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention.”); *Santarus v. Par Pharm*, 694 F.3d 1344, 1354 (Fed. Cir. 2012) (an obvious formulation does not “become patentable merely by testing and claiming an inherent property.”); *Metrics*,

*Inc. v. Senju Pharm. Co., Ltd.*, IPR2014-01043 [Paper No. 19, pg. 13] (“In our view, on this record, that degree of stability represents a ‘latent’ property of an otherwise obvious preparation . . .”).

**b. Claim 7**

Claim 7 differs from claim 1 in that it requires that greater than about 90% of the original amount of bromfenac remains in the claimed preparation after storage at about 60°C for 4 weeks and does not recite that the tyloxapol is present in an amount sufficient to stabilize the bromfenac. Claim 7 is obvious over Ogawa in view of Sallmann. The limitations of claim 7, which are common to claim 1, are obvious over Ogawa’s Example 6 in view of Sallmann’s Example 2 for the same reasons discussed above for claim 1. (EX1003, ¶ 53-55).

Claim 7’s recitation that “greater than about 90%” of the original bromfenac remains after storage at 60°C for 4 weeks is also described in Ogawa. (EX1004, 10:50-52, 14:45-50). Ogawa’s Example 6 was tested under the very same conditions (60°C for 4 weeks) as recited in claim 7 and, as shown in Table 11 of Ogawa, more than 90% of the original bromfenac in the preparation remained after 4 weeks. (EX1004, 10:50-52, 14:45-50). *Metrics, Inc. v. Senju Pharm. Co., Ltd.*, IPR2014-01043 [Paper No. 19, pg. 13] (noting a preparation of Ogawa modified by Sallmann would have exhibited the claimed stability).

A POSA would not expect that using tyloxapol instead of polysorbate 80 as the surfactant in Ogawa's Example 6 would have a negative impact on the amount of bromfenac remaining in the formulation after 4 weeks at 60°C. (EX1003, ¶¶ 63, 65, 69, 71-72). A POSA would reasonably expect that switching surfactants—employing the tyloxapol from Sallmann's Example 2 instead of polysorbate 80 in Ogawa's Example 6—would maintain greater than about 90% stability after 4 weeks at 60°C as recited in claim 7. (EX1003, ¶¶ 56, 63, 65, 69, 71-72).

**c. Claim 13**

Claim 13 differs from claim 1 in that it requires that the liquid preparation *does not contain mannitol* and does not recite that the tyloxapol is present in an amount sufficient to stabilize the bromfenac. Claim 13 is obvious over Ogawa in view of Sallmann. The limitations of claim 13 which are common to claim 1, are obvious over Ogawa's Example 6 in view of Sallmann's Example 2 for the same reasons discussed above for claim 1. (EX1003, ¶ 57-60). Further, neither Example 6 in Ogawa nor Example 2 in Sallmann contains mannitol. Thus, for the same reasons discussed above for claim 1, a POSA would have had a reasonable expectation of success in formulating a stable bromfenac/tyloxapol ophthalmic solution without mannitol. (EX1003, ¶ 61, 70).

**3. Dependent Claims**

The dependent claims merely recite, *inter alia*, pH ranges, and concentrations or ranges of ingredients or excipients (or lack thereof), which the '813 patent characterizes as “conventional.” (EX1001, 5:43-47). As explained further below, each of these dependent claims would have been *prima facie* obvious. Indeed, the Board has also found all dependent claims to be obvious in view of Sallmann and Ogawa. *Lupin Ltd. v. Senju Pharm. Co., Ltd.*, IPR2015-1105 [Paper No. 9, pp. 10-12]; *Lupin Ltd. v. Senju Pharm. Co., Ltd.*, IPR2015-01097 [Paper No. 9, p. 12].

**a. Claims 2, 8, and 14—Sodium Sulfite**

Claims 2, 8, and 14 recite the further requirement that the claimed aqueous liquid preparation further consists of sodium sulfite. (EX1001, 11:43-45, 12:13-15, 12:51-53). The aqueous formulation of Ogawa's Example 6 includes sodium sulfite. (EX1004, 10:5-18). Ogawa also generally discloses the use of sulfites, including sodium sulfite as part of the disclosure. (EX1004, 3:60-62). Based on at least these disclosures of Ogawa, a POSA would have been motivated to include sodium sulfite to the formulation. A POSA would have had a reasonable expectation of successfully formulating a stable ophthalmic formulation with bromfenac, tyloxapol, and sodium sulfite. (EX1003, ¶ 82). Given the results observed in Ogawa's Example 6, a POSA would have expected a similar result by adding sodium sulfite similar to the formulations claimed in claims 1, 7, and 13, which are similar to the formulation in Ogawa's Example 6. (EX1003, ¶ 82).



**b. Claims 3 and 15—Sodium Salt of Bromfenac**

Claims 3 and 15 recite the further requirement that the pharmacologically acceptable salt of bromfenac is a sodium salt of bromfenac. (EX1001, 11:46-48; 12:54-56). Like the challenged claims, Example 6 of Ogawa expresses a clear preference for the sodium salt of bromfenac in every working example. Thus, a POSA would have had a reason to select the bromfenac sodium salt of Ogawa. (EX1004, 10:8-9; EX1003, ¶ 84). For this same reason, POSA would have had a reasonable expectation of success in employing the sodium salt of bromfenac. (EX1003, ¶ 84). Accordingly, these dependent claims are obvious.

**c. Claims 4, 6, 10, 12, 16, 18, 21, 23, —Bromfenac Sodium and Tyloxapol Concentrations and Additional Additives**

Several of these dependent claims, claims 6, 10, 12, 16, 18, 21, and 23, further recite concentrations of the sodium salt of bromfenac, concentrations of tyloxapol, and/or recite additional additives. These additional features, however, do not alter the conclusion that these claims are obvious.

**(i) Bromfenac Sodium Concentration**

Dependent claims 6, 10, 12, 16, 18, 21, and 23 recite a bromfenac sodium salt concentration of a certain range. Dependent claims 6 and 18 further specify that the bromfenac sodium concentration is about 0.02 w/v % to about 0.1 w/v %. Dependent

claims 10, 12, 16, 21, and 23 further specify that the bromfenac sodium concentration is about 0.05 w/v % to about 0.1 w/v %.

Example 6 of Ogawa contains bromfenac sodium salt at a concentration of 0.1 w/v %, which is within the ranges recited in these dependent claims. (EX1004, 4:42-46, 10:8-9). Further, Ogawa discloses that the concentration of the active ingredient in the liquid preparation of the claimed invention may range from about 0.001% to about 10%. (EX1004, 4:42-46; EX1003, ¶ 94). Since Ogawa's disclosure of 0.1 w/v % of bromfenac sodium salt is a species within the genus of claimed bromfenac sodium salt ranges, this limitation does not impart patentability. *Chapman v. Casner*, 315 Fed. App'x 294, 297-98 (Fed. Cir. 2009). Additionally, because the claimed bromfenac sodium salt concentration ranges overlap with the concentration described in Ogawa, the ranges would have been obvious. *Iron Grip Barbell Co., Inc., v. USA Sports, Inc.*, 392 F.3d 1317, 1322 (Fed. Cir. 2004).

Further, the '813 patent does not describe any criticality associated with the claimed concentration ranges, the prior art does not teach away from the claimed ranges, and there are no unexpected results or other pertinent objective indicia attributable to the specific claimed bromfenac sodium salt concentration ranges sufficient to overcome the conclusion that these claims are obvious. *Galderma Labs., L.P., v. Tolmar, Inc.*, 737 F.3d 731, 737-738 (Fed. Cir. 2013). *See also InnoPharma Licensing Inc., et al. v. Senju Pharmaceutical Co., Ltd.*, IPR2015-

00902 [Paper No. 17, p. 14] (“[W]here the challenged claims reflect ranges that do not overlap the prior art ranges, they are close enough that an ordinary artisan would have expected them to have the same properties. . . . [A]n ordinary artisan would have arrived at the specified range using only routine experimentation.”).

**(ii) Tyloxapol Concentration**

Dependent claims 4, 6, 10, 16, and 21 recite a tyloxapol concentration of “about 0.01 w/v % to about 0.05 w/v %.” Claim 12 and 18 recite concentrations of “about 0.02 w/v %” and “about 0.02 w/v % to about 0.05 w/v %,” respectively.

Sallmann’s Example 2 discloses a tyloxapol amount of 1.0 mg/ml, which equates to a concentration of 0.1 w/v %, and Sallmann generally describes a range from 0.01 w/v % to 500 w/v % in an ophthalmic formulation containing 0.1 w/v % diclofenac. (EX1009, 8:10, 4:65-67; EX1003, ¶ 91). As discussed above, a POSA would have combined the teachings of Ogawa and Sallmann to modify Example 6 in Ogawa to substitute tyloxapol for polysorbate 80. A POSA would have had a reason to substitute tyloxapol for polysorbate 80 in Ogawa’s ophthalmic bromfenac formulation because Sallmann teaches that tyloxapol is a preferred solubilizer. (EX1009, 4:62; EX1003, ¶¶ 71-75).

Although the tyloxapol concentration utilized in Sallmann’s Example 2 does not overlap with the claimed tyloxapol range of claims 4, 6, 10, 12, 16, 18, and 21, a *prima facie* case of obviousness exists where, as here, the claimed ranges and prior

art ranges do not overlap but are close enough that a POSA would have expected them to have the same properties. (EX1003, ¶ 91). *Titanium Metals Corp. of Amer. v. Banner*, 778 F.2d 775 (Fed. Cir. 1985); *Lupin Ltd. v. Senju Pharm. Co., Ltd.*, IPR2015-01105 [Paper No. 9, p. 11] (finding the claimed tyloxapol concentration range to be addressed by Sallmann and Ogawa); *InnoPharma Licensing Inc., et al. v. Senju Pharm. Co., Ltd.*, IPR2015-00902 [Paper No. 17, p. 14] (finding that the prior art ranges “are close enough that an ordinary artisan would have expected them to have the same properties”).

Alternatively, because the claimed tyloxapol range falls within Sallmann’s generally disclosed range, Petitioner has established a *prima facie* case that the tyloxapol ranges of claims 4, 6, 10, 12, 16, 18, and 21 are obvious. The obviousness of these claims cannot be rebutted because: (i) the prior art does not teach away from the claimed ranges; and (ii) there is no indication that the claimed ranges are critical. (EX1001, Table 1). *Galderma Labs., L.P.*, 737 F.3d at 737-38.

Further, a POSA would have arrived at a tyloxapol concentration of the claimed ranges using only routine experimentation based on the disclosure of Sallmann. (EX1003, ¶ 92). *Aller*, 220 F.2d at 458; *Peterson*, 315 F.3d at 1330. Indeed, Sallmann gives express instructions for relevant considerations for the POSA to make these routine modifications. (EX1009, 4:62-35) (“Another 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.”**) (emphasis added).

Moreover, there is no evidence in the ’813 patent or its file history of any criticality associated with the recited ranges of tyloxapol. Nor is there any evidence that the claimed ranges achieve unexpected results over the prior art. As such, the obviousness cannot be rebutted. *InnoPharma Licensing Inc., et al. v. Senju Pharmaceutical Co., Ltd.*, IPR2015-00902 [Paper No. 17, p. 14] (finding that a POSA would have arrived at the specified range through routine experimentation).

### **(iii) Additional Additives**

In addition to reciting a bromfenac sodium salt concentration and/or a tyloxapol concentration as discussed above, claims 6, 12, 18, and 23 also recite certain additives: EDTA sodium salt; polyvinylpyrrolidone; and sodium sulfite. Claims 6, 12, 18, and 23 also state that “the stable aqueous liquid preparation *consists of*,” thereby excluding ingredients not specified in the claim from the scope. However, such “additive” limitations also do not render these claims patentable over the prior art because they are conventional and well-known for use in aqueous ophthalmic preparations. (EX1003, ¶¶ 94-99). *See, e.g., KSR*, 550 U.S. at 415-16 (“The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.”).

For example, Ogawa describes that it would have been desirable to use a solution containing: (i) the thickener polyvinyl pyrrolidone (PVP) to act as a carrier; (ii) the stabilizer sodium sulfite to prevent oxidation reactions; and (iii) a chelating agent, such as EDTA sodium salt. (EX1004, 3:54-58; 3:60-62; 4:33-34; 10:5-18; EX1003, ¶ 96).

Indeed, Example 6 of Ogawa includes each of these components with the exception of substituting tyloxapol for the polysorbate 80 (the inclusion of which would be rendered obvious by Sallmann). (EX1004, 10:12-16).<sup>5</sup> Furthermore, the resulting formulation, rendered obvious by the prior art, “consists of” the ingredients recited in the claim because it contains no additional ingredients that materially affect the alleged basic and novel characteristics.

Ogawa’s Example 6 contains BAC. Claims 6, 12, 18, and 23 exclude the use of BAC because the claimed stable aqueous liquid preparation “consists of” the recited ingredients. Ogawa teaches that “microbicidal agent or preservative . . . *may be added* to the compositions” and that “preservatives can be used.” (EX1004, 4:21-

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<sup>5</sup> Patent Owner has taken the position that under *Phillips* the terms “sodium edetate” and “EDTA sodium salt” includes disodium edetate. (See, e.g., EX1024 at 14). Under the broadest reasonable construction, then Patent Owner must also concede that EDTA sodium salt includes disodium edetate.

26, 4:64-65). Because Ogawa teaches the preservative is optional, these claims would have been obvious. (EX1003, ¶ 97). Similarly, Sallmann discloses that it would have been desirable to use a solution containing: (i) the thickener PVP to act as a carrier; (ii) the stabilizer sodium hydrogen sulfite to prevent oxidation reactions; and (ii) the chelating agent disodium edetate. (EX1009, 8:1-15, 4:23-30, 5:47-53; EX1003, ¶ 99).

Accordingly, each of Ogawa and Sallmann expressly teaches each of the additives recited in claims 6, 12, 18, and 23. Thus, because the prior art clearly disclosed desirability of relevant aqueous solutions containing the recited additives, a POSA would have had a reasonable expectation of success to arrive at the solutions claimed therein, and those claims are obvious.

**d. Claims 5, 11, 17, and 22—pH Ranges**

Claims 5, 11, 17, and 22 recite pH ranges from “about 7.5 to about 8.5.” (EX1001, 11:51-53, 12:26-27, 12:61-62, 13:22-24). Ogawa’s Example 6 discloses a formulation that has a pH of 8, thus Ogawa meets this additional limitation. Further, these pH limitations do not render these claims patentable over the prior art, as they are not only previously disclosed but are common and conventional pH ranges for ophthalmic preparations. (EX1003, ¶¶ 101-103). For example, Ogawa expressly discloses a preferred pH from about 7.5 to about 8.5 for the disclosed formulations. (EX1004, 3:48-53; EX1003, ¶ 101). Sallmann also discloses a

preferred pH range from 6.8 to 8.1. (EX1009, 5:14-16). Other references similarly describe a pH range that is within the claimed range. (EX1002, 3:1:2; EX1017, 8:21). Overlapping ranges establish a *prima facie* case of obviousness. *In re Peterson*, 315 F.3d at 1329-30; *In re Woodruff*, 919 F.2d 1575, 1578 (Fed. Cir. 1990); *In re Malagari*, 499 F.2d 1297, 1303 (C.C.P.A. 1974). Because Ogawa discloses a pH that falls within the pH ranges of claims 6, 12, 18, and 24, those pH ranges are obvious and do not render the claimed preparations patentable. *Chapman*, 315 Fed. App'x at 297-98.

Additionally, Table 1 of the '131 patent shows that substituting tyloxapol for polysorbate 80 would not appreciably affect the pH of a sodium bromfenac ophthalmic solution. (EX1001, 7:35-52). Moreover, even if substituting tyloxapol for polysorbate 80 in the formulation of Example 6 of Ogawa would result in a pH outside of the claimed range, a POSA would have been motivated to adjust the pH of the solution to a value within the claimed range, to ensure compatibility with the tear fluids while maintaining stability of the formulation and the drug it contains, and would have had a reasonable expectation of success in doing so. Indeed, Ogawa discloses that the pH of its ophthalmic solutions is preferably adjusted to between 7.7 and 8.5 through, *e.g.*, the addition of sodium hydroxide or hydrochloric acid. (EX1004, 3:31-67).

**e. Claims 9, 19, and 20—Storage Stability**



Claims 9, 19, and 20 depend directly or indirectly on Claims 7 or 13 and recite particular storage stability requirements for the liquid preparation. As explained above, the combined teachings of Ogawa and Sallmann would have rendered obvious a stable formulation for use in a method of treating an inflammatory condition of the eye. (EX1003, ¶¶ 62-63).

As explained in connection with claim 7, *supra*, Ogawa's Example 6 was tested under the very same conditions (60°C for 4 weeks) as recited in claims 9, 19, and 20, and as shown in Table 11 of Ogawa more than 90% or 92% of the original bromfenac in the preparation remained after 4 weeks. (EX1004, 10:50-52, 14:45-50). Specifically, Ogawa Table 11 describes that Example 6 Ophthalmic Solution, after 4 weeks at 60°C, contains about 100% of the original amount of bromfenac sodium. (EX1004, 10:50-52, 14:45-50; EX1003, ¶ 106). Because Ogawa meets these stability limitations, claims 9, 19, and 20 are obvious for the same reasons discussed for claims 7 and 13, from which they depend. (EX1003, ¶¶ 105-106).

A POSA would not expect that using tyloxapol instead of polysorbate 80 as the surfactant in Ogawa's Example 6 would have a negative impact on the amount of bromfenac remaining in the formulation after 4 weeks at 60°C. (EX1003, ¶¶ 63, 65, 69, 71-72, 74). A POSA would reasonably expect that switching surfactants—employing the tyloxapol from Sallmann's Example 2 instead of polysorbate 80 in Ogawa's Example 6—would maintain greater than about 90% or 92% of the original

bromfenac after 4 weeks at 60°C. (EX1003, ¶¶ 63, 65, 69, 71-72, 74). *See also Metrics, Inc. v. Senju Pharmaceutical Co., Ltd.*, IPR2014-01043 [Paper No. 19, pg. 13] (noting a preparation of Ogawa and Sallmann would have the claimed stability).

Furthermore, regardless of an actual disclosure, this degree of stability represents a “latent” property of an otherwise obvious preparation—a preparation suggested by Ogawa and Sallmann—and the inventors’ mere recognition of that property does not render nonobvious the modified preparation of Ogawa and Sallmann. *Baxter*, 952 F.2d at 392; *Santarus*, 694 F.3d at 1354; *Metrics, Inc. v. Senju Pharmaceutical Co., Ltd.*, IPR2014-01043 [Paper No. 19, pg. 13] (“In our view, on this record, that degree of stability represents a ‘latent’ property of an otherwise obvious preparation . . .”).

**f. Claims 24-26—No Preservative**

Dependent claims 24-26 recite the further limitation that the aqueous liquid preparation “does not include any preservative.” (EX1001, 14:12-19). Although Ogawa’s Example 6 includes BAC, Ogawa teaches that a microbicidal agent or preservative . . . *may be added*” and that “preservatives can be used.” (EX1004, 4:21-26, 4:64-65) (emphasis added). Because the preservative in Ogawa is optional, it would have been obvious to remove the BAC from this preparation in order to provide a non-preserved preparation. (EX1003, ¶ 108).

Sallmann also lists preservatives among the “customary pharmaceutically acceptable excipients and additives known” to a POSA. (EX1004, 4:4-10). Sallmann further states that “[w]here appropriate, preservatives and/or other excipients are added to an ophthalmic composition.” (EX1004, 4:21-22). Accordingly, Sallmann also provides that the use of preservatives is optional and would further suggest that a POSA would have found it obvious to remove preservatives from ophthalmic formulations. (EX1003, ¶ 109). Therefore, claims 24-26 would have been obvious over the prior art.

**g. Claim 27—Additional Additives**

Dependent claim 27 recites that the aqueous liquid preparation “*optionally* further consisting of one or more additives selected from the group consisting of buffers, thickeners, stabilizers, chelating agents, and pH controlling agents.” (EX1001, 14:20-23).<sup>6</sup> The ’813 patent itself states that these are “conventional” additives thus would have been well-known in the art at the time. (EX1001, 5:43-

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<sup>6</sup> Use of the claim term “optionally” suggests that the recited component are not even required, thus not limiting the scope of the claim any further, rendering it obvious for the same reason as the claim from which it depends. *In re Johnston*, 435 F.3d 1381, 1384 (Fed. Cir. 2006) (“[O]ptional elements do not narrow the claim because they can always be omitted.”).

47;EX1003, ¶ 68, 82, 111). Ogawa discloses the use of such conventional additives in ophthalmic formulations: buffers (EX1004, 3:43-45), thickening agents (4:24), stabilizers (3:48-53), chelating agents (4:23-24), and pH controlling agents (3:62-67). Ogawa's Example 6 also discloses a buffer (boric acid and borax), a thickener (PVP), a stabilizer (sodium sulfite), and a chelating agent (disodium edetate). (EX1004, 10:5-18). Sallmann also discloses such conventional additives in ophthalmic formulations. (EX1009, 4:4-10, 4:18-21, 5:50-56, 8:9). Sallmann's Example 2 also discloses a buffer (tromethamine), a stabilizer ( $\gamma$ -cyclodextrin), a chelating agent (disodium edetate), a pH controlling agent (HCl), and also a tonicity enhancing agent (sorbitol). (EX1009, 8:1-15). Therefore, a POSA would have been motivated to use one or more of the additives recited in claim 27, because these were all additives routinely used in ophthalmic formulations. (EX1003, ¶ 97-99, 112). Thus, claim 27 is obvious over the prior art. Further, claim 27 recites the use of such additive is merely optional and does not have a limited effect on the scope. Accordingly, the features claimed in claim 27 should not be given patentable weight.

**C. Ground 2: Claims 1-27 Are Unpatentable Under 35 U.S.C. § 103(a) over Ogawa in light of Sallmann and Fu**

**1. Overview of Fu (EX1011)**

Ogawa and Sallmann are discussed above. Australian Patent No. AU-B-22042/88 ("Fu") (EX1011) was published on March 16, 1989 (§ 102(b) prior art).

Fu was not cited in the prosecution history of the '813 patent, however, several related foreign patent publications were cited corresponding to Fu, none of which, however, were relied upon in rejecting any claims pending during prosecution.

Fu is directed to an improved preservative system for ophthalmic formulations containing non-steroidal anti-inflammatory drugs (“NSAIDs”) that have a carboxyl (–COOH) group (*i.e.*, that are acidic), and lists ketorolac and diclofenac, among others, as NSAIDs. (EX1011, 9:20-24). Bromfenac is also an NSAID that contains a carboxyl (–COOH) group. (EX1003, ¶¶ 27, 29, 115).

Fu explains that at the time of their invention, BAC was “widely used in ophthalmic solutions, and [was] considered to be the preservative of choice.” (EX1003, ¶ 32; EX1011, 4:33-35). However, Fu further reported that BAC had proven to be incompatible with NSAIDs that contain a carboxyl group because of the formation of a complex between BAC and the carboxyl group, which reduces the activity of both BAC and the NSAID. (EX1003, ¶ 118; EX1011, 5:13-21). For example, when an ophthalmic solution was made with ketorolac (an NSAID with a carboxyl group), BAC and polysorbate 80 as a surfactant, the solution became cloudy or turbid after a short period of time, indicating that a complex had formed between BAC and the NSAID. (EX1003, ¶ 118; EX1011, 5:1-7, 5:13-21).

Fu solved this problem by including “a stabilizing amount of an ethoxylated octylphenol as a nonionic surfactant.” (EX1003, ¶ 119-120; EX1011, 6:8-12). The

specific examples of ethoxylated octylphenols given by Fu are Octoxynol 9, Octoxynol 12, Octoxynol 13 and Octoxynol 40. (EX1011, 12:1-12). More significantly, the non-ionic surfactant disclosed in Fu is in the class of ethoxylated octylphenols, the same class to which tyloxapol belongs. (EX1019, 1:1:1-2:1:2; EX1020, 1:2:1 & 2: Scheme 1; EX1011, 10:1-3; EX1003, ¶ 120).

Fu describes an experiment (Example 5) in which six formulations were tested for their stability under a variety of conditions. (EX1003, ¶ 115; EX1011, 20:9-22). The formulations contained ketorolac (an NSAID having a carboxyl group), BAC, and various surfactants: Octylphenol (Octoxynol 40), polysorbate 80 (Tween 80) or Myrj 52. (EX1011, 20:23-21:14).

	<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

The ethoxylated octylphenol formulations remained clear under all conditions, while the others became turbid under certain conditions. Fu also indicated that the Octoxynol 40 formulation has “a 2 year shelf life,” and that “[p]reservative efficacy is maintained throughout the 2 year shelf life.” (EX1011, 21:23-27). Thus, Fu suggests to one of skill in the art that for ophthalmic solutions

containing an NSAID with a carboxyl group, and BAC, greater stability can be obtained by using an ethoxylated octylphenol as the surfactant instead of polysorbate 80. (EX1003, ¶ 119-121).

## **2. Independent Claims 1, 7, and 13**

As discussed above with respect to independent claims 1, 7, and 13, a POSA would have combined the teachings of Ogawa and Sallmann to modify Example 6 in Ogawa to substitute tyloxapol for polysorbate 80. A POSA would have had a reason to substitute tyloxapol for polysorbate 80 in Ogawa's ophthalmic bromfenac formulation containing BAC because Sallmann teaches that tyloxapol is a preferred solubilizer. (EX1003, ¶¶ 71-74, 87, 98).

A POSA would have been further motivated in replacing polysorbate 80 with tyloxapol by the teachings of Fu. Fu's Example 5 discloses that ethoxylated octylphenols surfactants—the class to which tyloxapol belongs—are superior to polysorbate 80 in stabilizing aqueous liquid preparations of an NSAID and BAC. (EX1011, 18:5-28, 20:9:22; EX1003, ¶¶ 119-120). Thus, in light of Fu, a POSA would have had further reason to use the tyloxapol surfactant taught by Sallmann because Fu's disclosure would have indicated that tyloxapol would have been superior to the polysorbate 80 (as used in Example 6 of Ogawa). Moreover, a POSA would have had a reasonable expectation of success because tyloxapol and polysorbate 80 were used interchangeably, and Fu shows that ethoxylated

octylphenol surfactants disclosed therein worked even better than polysorbate 80. (EX1003, ¶¶ 35-37, 39-40, 74).<sup>7</sup> *Metrics, Inc. v. Senju Pharmaceutical Co., Ltd.*, IPR2014-01041 [Paper No. 19, pg. 12] (“Petitioner shows sufficiently that Fu discloses that ophthalmic preparations of NSAIDs and BAC, which contain octylphenols (the class to which tyloxapol belongs) as the non-ionic surfactants, are more stable than those containing polysorbate 80 as the non-ionic surfactant.”).

The remaining limitations of claims 1, 7, and 13 are discussed above in reference to the Ogawa and Sallmann. Therefore, claims 1, 7, and 13 would be obvious in light of Ogawa in light of Sallmann and Fu.

### **3. Dependent Claims**

The dependent claims would be obvious over Ogawa in view of Sallmann as discussed above, but Fu provides additional teachings that are relevant to the obviousness of the dependent claims. As an initial matter, because Fu provides additional motivation for a POSA to add the tyloxapol disclosed in Sallmann’s

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<sup>7</sup> The reasonable expectation of success would have been further substantiated because each of tyloxapol, polysorbate 80, and the ethoxylated octylphenol used in Fu were all used in the prior art to successfully formulate commercial ophthalmic NSAID preparations. (EX1003, ¶¶ 35-37, 39-40).



Example 2 to Ogawa's Example 6, the same argument applies to all dependent claims thereto which recite tyloxapol. Accordingly all dependent claims would be obvious over Ogawa in view of Sallmann and Fu for the reasons discussed above.

**a. Claims 4, 6, 10, 12, 16, 18, and 21—Tyloxapol Concentration**

In particular, dependent Claims 4, 6, 10, 16, and 21 recite a tyloxapol concentration of “about 0.01 w/v % 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 w/v % to about 0.05 w/v %.” As discussed above in Ground 1, Sallmann's Example 2 discloses a tyloxapol concentration of 0.1 w/v % and Sallmann generally describes a range from 0.01 w/v % to 500 w/v %. (EX1009, 8:1-30, 4:65-67; EX1003, ¶ 91). Thus, the claimed ranges and the concentrations disclosed in Sallmann fall within the claimed ranges, or are close enough that a POSA would have expected them to have the same properties. (EX1003, ¶ 91).

Fu expressly discloses using ethoxylated octylphenols surfactants at a concentration of 0.02 w/v %, which falls inside the ranges claimed in claims 4, 6, 10, 12, 16, 18, and 21. (EX1011, 16:15, 18:5-28, Examples 2 & 5; EX1003, ¶¶ 85, 105, 126). *Titanium Metals*, 778 F.2d at 781-82. More significantly, the non-ionic surfactant disclosed in Fu is in the class of ethoxylated octylphenols, the same class

to which tyloxapol belongs. (EX1019, 1:1:1-2; EX1025, 1:2:1, 2: Scheme 1; EX1011; EX1003, ¶ 85, 126).

Furthermore, a POSA would have used a tyloxapol concentration of 0.02 w/v % based on Fu, which discloses that 0.02 w/v % of a non-ionic surfactant in the same ethoxylated octylphenol class as tyloxapol is sufficient to stabilize an aqueous liquid preparation of an NSAID and BAC, and superior to polysorbate 80. (EX1011, 18:5-28, Examples 2 & 5; EX1003, ¶¶ 85, 105, 127). *Metrics, Inc. v. Senju Pharmaceutical Co., Ltd.*, IPR2014-01041 [Paper No. 19, pg. 17] (“[W]e are persuaded the Petitioner comes forward with evidence sufficient to establish that a person of ordinary skill in the art would have been prompted by Fu to include tyloxapol, in a concentration of ‘about 0.02 w/v %,’ *id.*, in the modified composition of Ogawa or Sallmann.”).

A POSA would have combined the teachings of Fu with that of Ogawa and Sallmann because Fu teaches that ophthalmic formulations of NSAIDs and BAC containing ethoxylated octylphenols (the class to which tyloxapol belongs) as the non-ionic surfactant are more stable than those containing polysorbate 80 as the non-ionic surfactant. (EX1011, Example 5; EX1003, ¶¶ 33, 74, 119-123). And a POSA would have had a reasonable expectation of success because tyloxapol and polysorbate 80 were used interchangeably, and Fu shows that ethoxylated

octylphenol surfactants disclosed therein worked even better than polysorbate 80. (EX1003, ¶¶ 35-40, 74, 123, 127).

Because both polysorbate 80 and tyloxapol are non-ionic surfactants that were used interchangeably in ophthalmic formulations in the prior art, the same reasonable expectation of success that a POSA would have had to arrive at claims 1, 7, and 13 applies to claims 4, 6, 10, 12, 16, 18, and 21 insofar as the tyloxapol concentration limitation is concerned. (EX1003, ¶¶ 35-37, 40-41, 75, 133-135). And there would have been a reasonable expectation of success because each of tyloxapol, polysorbate 80, and the ethoxylated octylphenol used in Fu were all used in the prior art to successfully formulate commercial ophthalmic NSAID preparations. (EX1003, ¶¶ 35-37, 39-40). For the same reasons, the results would have been predictable.

In sum, a POSA would have been motivated to use an amount of tyloxapol that falls within the claimed range according to the combined teachings of Sallmann and Fu. Accordingly, claims 5, 15, and 23 are obvious.

**D. Ground 3: Claims 1-27 Are Unpatentable Under 35 U.S.C. § 103(a) over Ogawa in light of Sallmann and Yasueda**

**1. Overview of Yasueda (EX1012)**

Ogawa and Sallmann are discussed above. U.S. Patent No. 6,274,609 (“Yasueda”) (EX1012) issued August 14, 2001 (§ 102(b) prior art). Yasueda was

cited in the prosecution history of the '813 patent, however, Yasueda was not relied upon in rejecting any claims during prosecution of the '813 patent. Yasueda discloses pranlukast compositions with various surfactants. (EX1012, Abstract). Pranlukast can be used to prepare aqueous eye drop formulations for the treatment of allergic diseases, including those relating to the eye such as vernal keratoconjunctivitis. (EX1012, 1:16-24, 4:25-27, 9:61-10:12, 11:15-33).<sup>8</sup> Like bromfenac, pranlukast is considered acidic. (EX1044, 22:2:3-23:1:1; EX1003, ¶ 41, n. 10; EX1053, 1 (“[B]romfenac used in the claimed preparation is an acidic ‘NSAID’ drug.”)). Yasueda described the difficulty of preparing aqueous formulations using pranlukast due to “very low water-solubility.” (EX1012, 1:30-35).

Tyloxapol improves stability by limiting the interaction of the acidic drug (i.e., pranlukast) with the cationic BAC. (EX1012, 6:55-7:20, 7:44-45; EX1003, ¶ 41, n. 10 (petitioner’s expert explaining that much like pranlukast, bromfenac forms insoluble complexes when combined with quaternary ammonium preservatives, such as BAC, in aqueous liquid preparations)). As Yasueda explains, “[t]he main object of the present invention is to promote solubilization or suspension of pranlukast in water, thereby providing an aqueous liquid pharmaceutical

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<sup>8</sup> Bromfenac is also used for the treatment of conjunctivitis, further showing the similarities of the two drugs. (EX1001, 1:19-41, 6:17-21).

composition containing higher concentration of pranlukast and having good properties.” (EX1012, 1:43-48).

Experiment 4 describes “[t]est[s] for stability of aqueous solutions of pranlukast,” where the stability of pranlukast solutions were studied with various surfactants including polysorbate 80 and tyloxapol. (EX1012, 6:47-48).

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	upt 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, 6:65-7:19). According to Experiment 4, solutions A-F were stored at 60°C for two weeks. After two weeks, the pranlukast in the solution was determined by HPLC and the residual rate calculated:

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). As Yasueda explains when tyloxapol was used as the surfactant, “the residual rate of pranlukast was more than 98% and was stable.” (EX1012, 7:34-37). Polysorbate 80 was not as effective as tyloxapol in stabilizing pranlukast solutions. (EX1012, 7:37-42). Accordingly, Yasueda suggests the advantage of using tyloxapol, instead of polysorbate 80, to stabilize an acidic drug (such as pranlukast). (EX1003, ¶ 41).

## 2. Independent Claims 1, 7, and 13

As discussed above with respect to independent claims 1, 7, and 13, a POSA would have combined the teachings of Ogawa and Sallmann to modify Example 6 in Ogawa to substitute tyloxapol for polysorbate 80. A POSA would have had a reason to substitute tyloxapol for polysorbate 80 in Ogawa’s ophthalmic bromfenac formulation **in the presence of BAC** because Sallmann teaches that tyloxapol is a preferred solubilizer. (EX1003, ¶¶ 72, 87, 98).

Replacing polysorbate 80 with tyloxapol would be further substantiated by teachings of Yasueda. Yasueda compared tyloxapol and polysorbate 80 in their ability to solubilize aqueous ophthalmic solutions containing an acidic drug (i.e.,

pranlukast). As Patent Owner has admitted to the USPTO, much like pranlukast, bromfenac is also an acidic drug. (EX1053, 1 (“[B]romfenac used in the claimed preparation is an acidic ‘NSAID’ drug.”); EX1023, 8; EX1003, ¶ 41, n. 10). Indeed, as Petitioner’s expert explains, based on the disclosure of Yasueda, an acidic drug like bromfenac (and diclofenac) would experience the same problem of forming insoluble complexes when combined with quaternary ammonium preservatives, such as BAC, as pranlukast. (EX1003, ¶ 41, n. 10). Indeed the ’813 patent admits as much, stating that “[BAC] and other quaternary ammonium compounds are generally considered to be incompatible with ophthalmic compositions of drugs with acidic groups, such as nonsteroidal anti-inflammatory drugs,” because “they form complexes with the charged drug compounds.” (EX1001, 1:57-62).

Yasueda demonstrated that tyloxapol was better than polysorbate 80 at stabilizing the ophthalmic formulations containing an acidic drug (*i.e.*, pranlukast). (EX 1012, 6:47-7:43, Tables 4 and 5; EX1003, ¶¶ 41, 75). Since bromfenac is also an acidic drug, in light of Yasueda, a POSA would have had further reason to use the tyloxapol surfactant taught by Sallmann because Yasueda’s disclosure would have indicated that tyloxapol would have been superior to the polysorbate 80 (as used in Example 6 of Ogawa).

Moreover, a POSA would have had a reasonable expectation of success because tyloxapol and polysorbate 80 were used interchangeably, and Yasueda

shows that tyloxapol worked even better than polysorbate 80. (EX1003, ¶¶ 35-37, 40-41, 75, 133-135).<sup>9</sup> Also, as discussed above, a POSA would have found it at least obvious to try to prepare an aqueous liquid bromfenac preparation comprising tyloxapol as claimed because tyloxapol was one of only a few surfactants shown to stabilize the pranlukast formulation better than polysorbate 80 in the Yasueda disclosure. (EX1012, 6:47-7:43; EX1003, ¶¶ 41, 75, 133-135). *Wm. Wrigley Jr. Co.*, 683 F.3d at 1364-1365. The remaining limitations of claims 1, 7, and 13 are discussed above in reference to Ogawa and Sallmann. Therefore, claims 1, 7, and 13 would be obvious in light of Ogawa in light of Sallmann and Yasueda.

### **3. Dependent Claims**

Yasueda provides additional teachings that are relevant to the obviousness of the dependent claims. As an initial matter, because Yasueda provides additional motivation for a POSA to add the tyloxapol disclosed in Sallmann's Example 2 to Ogawa's Example 6, the same argument applies to all dependent claims thereto which

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<sup>9</sup> The reasonable expectation of success would have been further substantiated because both tyloxapol and polysorbate 80 used in Yasueda were used in the prior art to successfully formulate commercial ophthalmic NSAID preparations. (EX1003, ¶¶ 35-37, 39-40).



recite tyloxapol. Accordingly all dependent claims would be obvious over Ogawa in view of Sallmann and Yasueda for the reasons discussed above.

**a. Claims 4, 6, 10, 12, 16, 18, and 21—Tyloxapol Concentration**

In particular, dependent Claims 4, 6, 10, 16, and 21 recite a tyloxapol concentration of “about 0.01 w/v % 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 w/v % to about 0.05 w/v %.” As discussed above in Ground 1, Sallmann’s Example 2 discloses a tyloxapol concentration of 0.1 w/v % and Sallmann generally describes a range from 0.01 w/v % to 500 w/v %. (EX1009, 8:1-30, 4:65-67; EX1003, ¶ 91). Thus, the claimed ranges and the concentrations disclosed in Sallmann fall within the claimed ranges, or are close enough that a POSA would have expected them to have the same properties. (EX1003, ¶ 91).

Yasueda recites a concentration range of the surfactant that is preferably 0.01 to 0.2 w/v % where the composition is an aqueous suspension. (EX1012, 3:10-15; EX1003, ¶ 138). Yasueda’s tyloxapol range overlaps with the tyloxapol ranges recited in claims 4, 6, 10, 12, 16, 18, and 21. Furthermore, a POSA would have found it obvious to use a tyloxapol concentration of 0.02 w/v % based on Yasueda. (EX1012, 3:10-15; EX1003, ¶ 138-140). A POSA would have combined the teachings of Yasueda with that of Ogawa and Sallmann because Yasueda teaches

that aqueous ophthalmic solutions containing tyloxapol as the non-ionic surfactant are more stable than those containing polysorbate 80 as the non-ionic surfactant. (EX1012, 7:34-42; EX1003, ¶ 133). A POSA would have had a reasonable expectation of success because tyloxapol and polysorbate 80 were used interchangeably, and Yasueda shows that tyloxapol worked even better than polysorbate 80. (EX1003, ¶¶ 133-135).

Because both polysorbate 80 and tyloxapol are non-ionic surfactants that were used interchangeably in ophthalmic formulations in the prior art, the same reasonable expectation of success that a POSA would have had to arrive at claims 1, 7, and 13 applies to claims 4, 6, 10, 12, 16, 18, and 21 insofar as the tyloxapol concentration limitation is concerned. (EX1003, ¶¶ 35-37, 40-41, 75, 133-135). And there would have been a reasonable expectation of success because tyloxapol and polysorbate 80 were both used in the prior art to successfully formulate commercial ophthalmic NSAID preparations. (EX1003, ¶¶ 35-37, 39-41). For the same reasons, the results would have been predictable.

In sum, a POSA would have been motivated to use an amount of tyloxapol that falls within the claimed range according to the combined teachings of Sallmann and Yasueda. Accordingly, claims 5, 15, and 23 are obvious.

#### **E. Objective Indicia of Nonobviousness**

Although objective indicia of nonobviousness must be taken into account, they do not necessarily control an obviousness determination. *Newell Cos., Inc. v. Kenney Mfg. Co.*, 864 F.2d 757, 768 (Fed. Cir. 1988). Petitioner addresses below potential objective indicia arguments that Patent Owner may attempt to raise. To the extent Patent Owner does assert any objective indicia in this proceeding, detailed consideration of Patent Owner’s evidence should not be undertaken until Petitioner has had an opportunity to respond to it. *Amneal Pharms., LLC v. Supernus Pharms., Inc.*, IPR2013-00368 [Paper 8, pp. 12-13].

**1. No Unexpected Results Over the Closest Prior Art**

To establish unexpected results, Patent Owner must compare its invention with the closest prior art. *In re De Blauwe*, 736 F.2d 699, 705 (Fed. Cir. 1984); *In re Merchant*, 575 F.2d 865, 868 (C.C.P.A. 1978). Ogawa discloses examples of ophthalmic formulations containing bromfenac, BAC, and the non-ionic surfactant polysorbate 80 (EX1004, 10:5-18; EX1003, ¶ 115) and, therefore, Ogawa is considered the closest prior art for this inquiry. Patent Owner’s self-serving argument during prosecution—that “there is no suggestion to avoid degradation of acidic drugs, such as bromfenac, by using tyloxapol” or applicant “surprisingly found that the degradation of bromfenac could be avoided by specifically including tyloxapol in the preparation”—fails to establish unexpected superiority against the teachings of Ogawa. (EX1023, 8; EX1025, 4; EX1003, ¶ 141). *See also Lupin Ltd.*

*v. Senju Pharm. Co., Ltd.*, IPR2015-01105 [Paper No. 9, p. 13] (“Patent Owner has not directed us to any description in the Specification of the ’813 patent, or in any other evidence of record, characterizing or otherwise establishing that the asserted superior results would have been ‘unexpected.’”); *InnoPharma Licensing Inc., et al. v. Senju Pharm. Co., Ltd.*, IPR2015-00902 [Paper No. 17, p. 16] (“The record is devoid of objective evidence in that regard. Not even the inventors described tyloxapol as ‘surprising’ or ‘unexpected’ in its stabilizing effect . . . .”); *Metrics, Inc. v. Senju Pharm. Co., Ltd.*, IPR2014-01041 [Paper No. 19, pg. 14].

**a. Tyloxapol’s Stabilizing Effects**

Tyloxapol’s stabilizing effects described in the ’813 patent are not unexpected. The patentees allege in the ’813 patent that liquid aqueous preparations of bromfenac formulated with tyloxapol exhibit greater bromfenac stability than those formulated with polysorbate 80. (EX1001, 7:57-62). The stabilizing property of tyloxapol was well-known in the prior art and was not “unexpected,” for the reasons already discussed above. (EX1003, ¶ 142).

Furthermore, the prior art taught that non-ionic surfactants in the same *ethoxylated octylphenol* family as tyloxapol, such as Octoxynol 9 and Octoxynol 40, stabilized ophthalmic formulations of NSAIDs and BAC. (EX1011, 20:23-27; EX1003, ¶¶ 115, 120-122, 143). Tyloxapol is, and was known in the prior art as, an oligomeric form of Octoxynol 9. (EX1019, 1:1:2; EX1020, 1:2:1; EX1003, ¶¶ 121-

123, 144). Ethoxylated octylphenol surfactants, a class that includes tyloxapol, were known to be superior to polysorbate 80 in stabilizing aqueous liquid preparations of NSAIDs and BAC. (EX1011, 18:5-28, 20:9-22; EX1003, ¶¶ 119-120, 143, 145-146). Accordingly, at least for these reasons, the prior art shows that the stabilizing effect of tyloxapol was not unexpected, but rather, *expected*.

#### **b. Scope of Stabilizing Effects**

Patent Owner has not demonstrated that any purported unexpected results attributable to tyloxapol, including its stabilizing effects, occur over the entire claimed range of aqueous liquid bromfenac preparations. *In re Peterson*, 315 F.3d at 1331. For example, the claims of the '813 patent encompass preparations having a wide pH range—spanning from at least 7.5 to 8.5. But the patent provides the stability analysis of tyloxapol at a very small range of 8.16, 8.17 and 8.19. There is no indication that tyloxapol provides the same stability at other pH ranges. (EX1003, ¶¶ 148-149). *See also Lupin Ltd. v. Senju Pharm. Co., Ltd.*, IPR2015-01097 [Paper No. 9, p. 18]; *Metrics, Inc. v. Senju Pharm. Co., Ltd.*, IPR2014-01041 [Paper No. 19, pg. 15].

#### **2. Other Objective Indicia**

First, Patent Owner cannot establish that the claims of the '813 patent met any long-felt, but unmet, need. Bromfenac ophthalmic formulations existed (Xibrom<sup>®</sup> and Bromday<sup>®</sup>) prior to Prolensa<sup>®</sup>, the purported commercial embodiment of certain

of the claims of the '813 patent. (EX1003, ¶¶ 44, 150-152). Further, the long-felt, but unmet, need should be a need created by inadequacies in the technical knowledge, not by business-driven market forces that are unrelated to technical considerations. *Friskit, Inc. v. Real Networks, Inc.*, 306 F. App'x 610, 617-618 (Fed. Cir. 2009). To the extent there was even any need for the claimed bromfenac ophthalmic formulations claimed in the '813 patent, it would have been met by the disclosures of Ogawa and Hara, each of which describes stable ophthalmic bromfenac formulations. (EX1003, ¶ 151). And Bronuck®, which was commercially available in July 2000, was a stable formulation. (EX1002, 2:Title & 3:1:2). Bronuck® is a commercial embodiment of Ogawa. (EX1003, ¶ 151).

Patent Owner cannot demonstrate that the claimed bromfenac preparations were met with skepticism or that other POSAs tried but failed to solve the problem allegedly solved by the '813 patent. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1540 (Fed. Cir. 1983). Any evidence of failure of others must suggest that the prior attempts failed because they lacked the claimed elements. *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1313 (Fed. Cir. 2006). A stable ophthalmic bromfenac formulation was commercially launched in July 2000. (EX1002, 2:Title). At least for this reason, there can be no genuine skepticism. (EX1003, ¶¶ 153-154).

Patent Owner cannot show that the claimed invention of the '813 patent was met with any praise in the industry. Stable bromfenac ophthalmic formulations were

already marketed in products relating to the prior art (EX1003, ¶¶ 43-44, 155) and the prior art disclosed similar stable formulations. (EX1003, ¶¶ 36-39). *See also Lupin Ltd. v. Senju Pharm. Co., Ltd.*, IPR2015-01105 [Paper No. 9, p. 14].

Next, a showing of “copying in the ANDA context where a showing of bioequivalence is required for FDA approval” is not compelling evidence of nonobviousness. *Purdue Pharma Prods. L.P. v. Par Pharm., Inc.*, 377 Fed App’x 978, 983 (Fed. Cir. 2010); *see also Lupin Ltd. v. Senju Pharm. Co., Ltd.*, IPR2015-01105 [Paper No. 9, p. 14].

Further, commercial acquiescence requires Patent Owner to show that any license in the ’813 patent arose out of recognition and acceptance of the patent and a nexus to the merits of the claimed invention. *Stratoflex, Inc.*, 713 F.2d at 1539. The ’813 patent has not received any special industry recognition, (EX1003, ¶ 155), and the Board has already found Patent Owner’s assertions of licenses to lack sufficient explanation to shown non-obviousness. *Lupin Ltd. v. Senju Pharm. Co., Ltd.*, IPR2015-01105 [Paper No. 9, p. 15].

Finally, commercial success requires Patent Owner to show that: (i) that a claimed embodiment (Prolensa®) is successful commercially, *e.g.*, has substantial market share; and (ii) there is a nexus between the success and the novel features of the claims. *Tokai Corp. v. Eason Enters., Inc.*, 632 F.3d 1358, 1369-70 (Fed. Cir.

2011). To date, Patent Owner has not come forward with any evidence of commercial success and the prosecution history is devoid of any such evidence.

## **IX. CONCLUSION**

Petitioner has demonstrated by a preponderance of the evidence that claims 1-27 of the '813 patent are unpatentable as obvious over the prior art combinations cited herein, and respectfully requests that the Board so finds.

RESPECTFULLY SUBMITTED,

ALSTON & BIRD LLP

Date: November 2, 2015

/Jitendra Malik/

Telephone: 919-862-2200  
Fax: 919-862-2260

Jitendra Malik (Reg. No. 55823)  
4721 Emperor Boulevard, Suite 400  
Durham, North Carolina 27703  
Jitty.Malik@alston.com  
*Lead Counsel for Petitioner*



### **CERTIFICATION OF SERVICE**

Pursuant to 37 C.F.R. §§ 42.6(e), 42.8(b)(4) and 42.105, the undersigned certifies that on the 2<sup>nd</sup> day of November 2015, a complete copy of the foregoing Petitioner's Petition for *Inter Partes* Review of U.S. Patent No. 8,871,813, Power of Attorney, and all supporting exhibits were served via UPS® to the Patent Owner by serving the correspondence address of record for the '813 patent:

WENDEROTH, LIND & PONACK, L.L.P.  
1030 15th Street, N.W.,  
Suite 400 East  
Washington, DC 20005-1503

Courtesy copies of the foregoing were also served via UPS® on lead counsel of record for the Patent Owner in *Lupin Ltd. et al. v. Senju Pharmaceutical Co., Ltd.*, IPR2015-01105 as follows:

Bryan C. Diner  
Finnegan, Henderson, Farabow, Garrett & Dunner LLP  
901 New York Avenue, NW  
Washington DC 20001-4413

Deborah H. Yellin  
CROWELL & MORING LLP  
Intellectual Property Group  
1001 Pennsylvania Avenue, N.W.  
Washington, DC 20004-2595

Respectfully submitted,

ALSTON & BIRD LLP

By: /Jitendra Malik/

Petition for *Inter Partes* Review  
of U.S. Patent No. 8,871,813

Jitendra Malik, Ph.D.  
Registration No. 55,823  
4721 Emperor Boulevard, Suite 400  
Durham, North Carolina 27703-8580  
(919) 862-2200

Hidetada James Abe  
Registration No. 61,182  
333 South Hope Street, 16th Floor  
Los Angeles, California 90071  
(213) 576-1000

Lance Soderstrom  
Registration No. 65,405  
90 Park Avenue  
15<sup>th</sup> Floor  
New York, New York 10016-1387  
212.210.9400

*Attorneys for Petitioners InnoPharma  
Licensing, Inc., InnoPharma Licensing LLC,  
InnoPharma Inc., InnoPharma LLC, Mylan  
Pharmaceuticals Inc., and Mylan Inc.*