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March 27, 2015

CONFIDENTIAL

VIA FEDEX OVERNIGHT DELIVERY[1]

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President & CEO
BAUSCH & LOMB INCORPORATED
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Re: ANDA No. 206326 (Bromfenac) Notification of Certification of Noninfringement and/or Invalidity for U.S. Patent No. 8,927,606 Pursuant to § 505(j)(2)(B)(ii) of the U.S. Federal Food, Drug and Cosmetic Act

To whom it may concern:

We represent Innopharma Licensing, Inc. ("Innopharma") in connection with this letter and in connection with any litigation that ensues therefrom. Pursuant to Section 505(j)(2)(B)(ii) of the Federal Food, Drug and Cosmetic Act and 21 C.F.R. § 314.95, Innopharma hereby provides notice that today it has amended Abbreviated New Drug Application No. 206326 ("ANDA") certifying, as described in

[1] Innopharma has obtained approval from the FDA to use Federal Express in lieu of the U.S. Postal Service for the purpose of providing notice to the NDA holder and any patent assignees associated with Paragraph IV certification(s) contained within ANDA 206326 (attached as Exhibit B). The assignee's name for the '606 patent is taken from the face page of the '606 patent. The USPTO's web-based assignment records accessed on March 27, 2015 report that the assignment data for the '606 patent is not currently available.

21 C.F.R. § 319.94(a)(12)(i)(A)(4) ("Paragraph IV"), that U.S. Patent No. 8,927,606 ("the '606 patent") is invalid, unenforceable, and/or will not be infringed by the manufacture, use, sale, offer for sale, or importation of Innopharma's Bromfenac Product as defined by Innopharma's ANDA No. 206326.

Innopharma's ANDA is for a generic drug product having the established name PROLENSA™. The active ingredient in the proposed drug product is bromfenac, which is present in the PROLENSA™ ophthalmic solution product in the form of bromfenac sodium sesquihydrate. PROLENSA™ is supplied as a sterile, aqueous 0.07% solution with a pH of 7.8.

The United States Food and Drug Administration ("FDA") has accepted Innopharma's ANDA for filing and has assigned the application No. 206326. The ANDA contains the required bioavailability and/or bioequivalence data from studies on Innopharma's Bromfenac Product that is the subject of the ANDA.

Innopharma originally submitted its ANDA under 21 U.S.C. § 355(j)(1) and (2)(A) with Paragraph IV certifications to U.S. Patent Nos. 8,129,431 ("the '431 patent") and the 8,669,290 ("the '290 patent"). On September 19, 2014, Innopharma sent to Senju Pharmaceuticals and Bausch & Lomb, written notification of its PIV certification and a detailed statement of its then-existing factual and legal bases of Innopharma's belief that each of the '431 and '290 patents is invalid, unenforceable, or will not be infringed by the manufacture, use, sale, offer for sale, or importation of the drug product described in Innopharma's ANDA. On October 30, 2014, Innopharma sent to Senju Pharmaceuticals and Bausch & Lomb, written notification of its amendment to Innopharma's ANDA to further include a PIV certification to U.S. Patent No. 8,754,131 ("the '131 patent") and a detailed statement of its then-existing factual and legal bases of Innopharma's belief that the '131 patent is invalid, unenforceable, or will not be infringed by the manufacture, use, sale, offer for sale, or importation of the drug product described in Innopharma's ANDA. Innopharma has amended its ANDA under 21 C.F.R. § 314.94(a)(12)(vi) to further include a Paragraph IV certification to the '606 patent, which lists as an issuance date on its face of January 6, 2015. Each of the '431, '290, '131 and '606 patents is listed in Approved Drug Products with Therapeutic Equivalence Evaluations ("the Orange Book") in connection with Bausch & Lomb, Inc.'s ("B&L") approved NDA No. 203168 for PROLENSA™ ophthalmic solution.

Innopharma seeks the FDA's approval to market its proposed Bromfenac Product prior to the expiration of the Orange Book Patents. Innopharma alleges, and originally certified to the FDA that, to the best of Innopharma's knowledge, the '431 and '290 patents are invalid, unenforceable, and/or will not be infringed by the manufacture, use, sale, offer for sale, or importation of the drug product described in Innopharma's ANDA. Innopharma additionally alleges and has certified to the FDA that, to the best of Innopharma's knowledge, the '131 patent is invalid, unenforceable, and/or will not be infringed by the manufacture, use, sale, offer for sale, or

importation of the drug product described in Innopharma's ANDA. Further, Innopharma additionally alleges and has certified to the FDA that, to the best of Innopharma's knowledge, the '606 patent is invalid, unenforceable, and/or will not be infringed by the manufacture, use, sale, offer for sale, or importation of the drug product described in Innopharma's ANDA. With regard to the '606 patent, according to the FDA's Orange Book:

- the '606 patent will expire on January 16, 2024.

Attached as Exhibit A is a detailed statement, made pursuant to 21 U.S.C. § 355(j)(2)(B)(iv)(II) and 21 C.F.R. § 314.95, of the present factual and legal bases for Innopharma's Paragraph IV certification to the '606 patent of the Orange Book Patents. The statements made therein are based on the information currently available to Innopharma. Innopharma reserves all rights to raise any additional defenses relating to invalidity, unenforceability, and/or noninfringement should additional information become known to Innopharma.

Offer of Confidential Access to ANDA

Pursuant to 21 U.S.C. § 355(j)(5)(C), this notice letter includes an Offer of Confidential Access to Innopharma's ANDA and any supplement(s) thereto. As required by Section 355(j)(5)(C)(i)(III), Innopharma offers to provide confidential access to certain information from its ANDA No. 206326 for the sole and exclusive purpose of determining whether an infringement action referred to in Section 355(j)(5)(B)(iii) can be brought.

Section 355(j)(5)(C)(i)(III) allows Innopharma to impose restrictions "as to persons entitled to access, and on the use and disposition of any information accessed, as would apply had a protective order been entered for the purpose of protecting trade secrets and other confidential business information." That provision also grants Innopharma the right to redact its ANDA to exclude non-relevant information in response to a request for Confidential Access under this Offer.

As permitted by statute, Innopharma imposes the following terms and restrictions on its Offer of Confidential Access:

(1) Innopharma will permit confidential access to certain information from its proprietary ANDA No. 206326 to attorneys from one outside law firm representing B&L; provided, however, that such attorneys do not engage, formally or informally, in any patent prosecution for B&L or any FDA counseling, litigation, or other work before or involving the FDA. Such information (hereinafter, "Confidential Innopharma Information") shall be marked with the legend "CONFIDENTIAL INNOPHARMA INFORMATION."

(2) The attorneys from the outside law firm representing B&L shall not disclose any Confidential Innopharma Information to any other person

or entity, including B&L employees, outside scientific consultants, and/or other outside counsel retained by B&L, without the prior written consent of Innopharma.

(3) As provided by Section 355(j)(5)(C)(i)(III), B&L's outside law firm shall make use of the Confidential Innopharma Information for the sole and exclusive purpose of determining whether an action referred to in Section 355(j)(5)(B)(iii) can be brought and for no other purpose. By way of example only, the Confidential Innopharma Information shall not be used to prepare or prosecute any future or pending patent application by B&L in connection with any filing to, or communication with, the FDA relating to Innopharma's ANDA No. 206326. B&L's outside law firm agrees to take all measures necessary to prevent unauthorized disclosure or use of the Confidential Innopharma Information, and that all Confidential Innopharma Information shall be kept confidential and not disclosed in any manner inconsistent with this Offer of Confidential Access.

(4) The Confidential Innopharma Information disclosed is, and remains, the property of Innopharma. By providing said Confidential Innopharma Information, Innopharma does not grant B&L and/or its outside law firm any interest in or license for and to the Confidential Innopharma Information.

(5) B&L's outside law firm shall, within thirty-five (35) days from the date that it first receives the Confidential Innopharma Information, return to Innopharma all Confidential Innopharma Information and any copies thereof. B&L's outside law firm shall return all Confidential Innopharma Information to Innopharma before any infringement suit is filed by B&L, if suit is commenced before this 35-day period expires. In the event that B&L opts to file suit, none of the information contained in or obtained from any Confidential Innopharma Information that Innopharma provides, including Exhibit A to this letter, shall be included in any publicly-available complaint or other pleading.

(6) Nothing in this Offer of Confidential Access shall be construed as an admission by Innopharma regarding the validity, enforceability, and/or infringement of any U.S. patent. Further, nothing herein shall be construed as an agreement or admission by Innopharma with respect to the competency, relevance, or materiality of any such Confidential Innopharma Information, document, or thing. The fact that Innopharma provides Confidential Innopharma Information to B&L upon B&L's request shall not be construed as an admission by Innopharma that such Confidential Innopharma Information is relevant to the disposition of any issue relating to any alleged infringement of the Orange Book Patents or to the validity or enforceability of any or all of these patents.

(7) The attorneys from B&L's outside law firm shall acknowledge in writing their receipt of a copy of these terms and restrictions prior to production of any Confidential Innopharma Information. Such written acknowledgement shall be provided to the undersigned.

(8) This Offer of Confidential Access shall be governed by the laws of the State of New Jersey, USA.

Section 355(j)(5)(C)(i)(III) provides that any request for access that B&L makes under this Offer of Confidential Access "shall be considered acceptance of the offer of confidential access with restrictions as to persons entitled to access, and on the use and disposition of any information accessed, contained in [this] offer of confidential access" and that the "restrictions and other terms of [this] offer of confidential access shall be considered terms of an enforceable contract." Thus, to the extent that B&L requests access to Confidential Innopharma Information, it necessarily accepts the terms and restrictions outlined above.

Written notice requesting access under this Offer of Confidential Access should be made to:

Deepro R. Mukerjee
Alston & Bird LLP
90 Park Avenue
New York, New York 10016
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Fax: (212) 210-9444
deepro.mukerjee@alston.com

By providing this Offer of Confidential Access, Innopharma maintains the right and ability to bring and maintain a Declaratory Judgment action under 28 U.S.C. § 2201 *et seq.*, pursuant to 21 U.S.C. § 355(j)(5)(C).

Copies of this letter and the attached exhibits are also being provided by U.S. Registered mail, return receipt requested.

Sincerely,

Deepro R. Mukerjee

Enclosures: Exhibits A & B

EXHIBIT A

Table of Contents

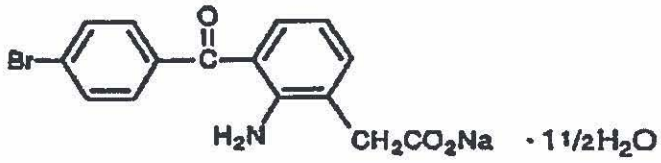
EXHIBIT A
DETAILED STATEMENT OF THE FACTUAL AND LEGAL BASIS FOR INNOPHARMA LICENSING INC.'S CERTIFICATION THAT U.S. PATENT NO. 8,927,606 IS INVALID, UNENFORCEABLE, AND/OR WILL NOT BE INFRINGED BY THE MANUFACTURE, USE, SALE, OFFER FOR SALE, OR IMPORTATION OF INNOPHARMA'S BROMFENAC PRODUCT AS DEFINED BY ANDA NO. 206-326

For at least the reasons set forth below, U.S. Patent No. 8,927,606 ("the '606 patent") does not prohibit Innopharma Licensing Inc. ("Innopharma") from manufacturing, using, selling, offering for sale, or importing Innopharma's Bromfenac Product as covered by ANDA No. 206-326 after the FDA approves its ANDA.[1]

I. Introduction

Bausch & Lomb ("B&L") markets an ophthalmic solution having an active agent known as bromfenac under the name PROLENSA™. Bromfenac is a nonsteroidal anti-inflammatory drug (NSAID) for ophthalmic use. The FDA has approved PROLENSA™ for the treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract surgery. Exhibit 1, *PROLENSA™ Label.*

PROLENSA™ is formulated as bromfenac sodium sesquihydrate. The USAN name for bromfenac sodium sesquihydrate is bromfenac sodium. The standard chemical name for bromfenac sodium is sodium [2-amino-3-(4-bromobenzoyl)phenyl] acetate sesquihydrate. It has an empirical formula of $C_{15}H_{11}BrNNaO_3 \cdot 1\frac{1}{2} H_2O$. The structural formula for bromfenac sodium is:



The Orange Book lists the following patents for PROLENSA™: the '606 patent; U.S. Patent No. 8,128,431 ("the '431 patent"); U.S. Patent No. 8,475,131 ("the '131 patent"); U.S. Patent No. 8,871,813 ("the '813 patent"); and U.S. Patent No. 8,669,290 ("the '290 patent") (collectively, "the Orange Book Patents"). The Orange Book also indicates that PROLENSA™ is associated with New Drug Application No. 203-168, which is held by B&L. The FDA has approved NDA No. 203-168 for PROLENSA™ 0.07% ophthalmic solution.

[1] Innopharma reserves its rights to raise any additional defenses relating to invalidity, unenforceability, and non-infringement in any and all proceedings for alleged patent infringement.

Innopharma hereby incorporates by reference all prior Notification letters, including those dated September 19, 2014 and October 30, 2014, and related exhibits, the combined contents of which provided notice to the NDA holder and assignee of the '431, '131, and '290 patents and set forth the factual and legal bases for Innopharma's certification that the '431, '131, and '290 patents are invalid, unenforceable, and/or will not be infringed by the manufacture, use, sale, offer for sale, or importation of Innopharma's Bromfenac Product as defined by ANDA No. 206-326.

II. Summary

Innopharma's manufacture, use, sale, offer for sale, or importation of its Bromfenac Product will not infringe any of the claims of the '606 patent for at least the following reasons:[2]

The '606 Patent

As set forth in detail below, Innopharma cannot infringe claims 1-30 of the '606 patent because each of these claims is invalid under 35 U.S.C. § 103 as follows:

- Each of claims 1-30 of U.S. Patent Number 8,927,606 is invalid as obvious in light of U.S. Patent No. 4,910,225 ("the '225 patent") in view of WO 02/13804 ("the '804 publication"); U.S. Patent Number 5,414,011 ("the '011 patent"); and Regev, *Journal of Colloid and Interface Science* 210, 8–17 (1999) ("Regev").

- Each of claims 1-30 of U.S. Patent Number 8,927,606 is invalid as obvious in light of the'225 patent in view of the '804 publication; the '011 patent; Yuan et al., *J. Phys. Chem. B* 2001, 105, 4611-4615 ("Yuan") and U.S. Patent No. 2,454,541 (the '541 patent).

- Each of claims 1-30 of U.S. Patent Number 8,927,606 is invalid as obvious in light of the '225 patent in view of U.S. Patent No. 6,107,343 ("the'343 patent") and U.S. Patent No. 6,274,609 ("the '609 patent").

- Each of claims 1-30 of U.S. Patent Number 8,927,606 is invalid as obvious in light of the'343 patent in view of the '225 patent and Hara, Yoshiyuki, *Clinics & Drug Therapy*, 2002, 19:1014-1015 ("Hara").

[2] In addition to the reasons of invalidity set forth in this Exhibit A, Innopharma incorporates by reference, and reserves the right to assert, any invalidity positions set forth in any *inter partes* review related to any patent at issue.

III. Analysis

A. General Legal Principles

1. Burdens and Presumptions

Each claim of a patent issued by the United States Patent and Trademark Office ("PTO") is presumed to be valid; this presumption is independent of the validity of other claims. 35 U.S.C. § 282. A party may overcome this presumption by presenting clear and convincing evidence of a patent's invalidity. *See, e.g., Beckson Marine, Inc. v. NFM, Inc.*, 292 F.3d 718, 725 (Fed. Cir. 2002). The presumption of validity includes a "presumption of nonobviousness which the patent challenger must overcome by proving facts with clear and convincing evidence." *See e.g., Apotex USA, Inc. v. Merck & Co.*, 254 F.3d 1031, 1036 (Fed. Cir. 2001).

The "clear and convincing evidence" standard of proof applies even if the prior art under consideration was not previously considered by the PTO during prosecution. *Microsoft Corp. v. i4i Ltd. Partnership*, 131 S.Ct. 2238, 2250 (2011). A patent may also be found invalid based upon prior art already considered by the examiner if it can be shown through clear and convincing evidence that the examiner erred in interpreting or applying the prior art. Thus, after due consideration of the presumption of validity, a trial court is free to come to a different conclusion of patentability from the PTO on the basis of evidence before the court. *See, e.g., Purdue Pharma L.P. v. Faulding, Inc.*, 230 F.3d 1320, 1329 (Fed. Cir. 2000); *AK Steel Corp. v. Sollac & Ugine*, 344 F.3d 1234, 1245 (Fed. Cir. 2003).

2. Claim Construction

The first step in an invalidity or non-infringement analysis is to construe the claims of the patent. *See, e.g., Rapoport v. Dement*, 254 F.3d 1053, 1058 (Fed. Cir. 2001). The general rule is that claim language is given its ordinary and accustomed meaning as understood by one of ordinary skill in the art, unless the patentee ascribed a different meaning to a claim in either the specification or the prosecution history. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312, 1321 (Fed. Cir. 2005). Claim interpretation involves consideration of the language of the patent claim itself, the other claims, the specification, the prosecution history, and extrinsic evidence if necessary. *See, e.g., Phillips*, 415 F.3d at 1312; *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996); *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 979-80 (Fed. Cir. 1995) *(en banc) ("Markman I")*. When construing a claim, a court principally consults the evidence intrinsic to the patent: the claims themselves, the specification, and the prosecution history. *Phillips*, 415 F.3d at 1317; *Vitronics*, 90 F.3d at 1582-83. Usually, analysis of the intrinsic evidence suffices to enable one to determine the meaning of claim terms. *Vitronics*, 90 F.3d at 1582. If the intrinsic evidence resolves ambiguity in a disputed claim, extrinsic evidence cannot be used to contradict the established meaning of the claim language. *See, e.g., Mantech Envtl. Corp. v. Hudson Envtl. Servs.*, 152 F.3d 1368, 1373 (Fed. Cir. 1998); *Bell & Howell Document Mgmt. Prods. Co. v. Altek Sys.*, 132 F.3d 701, 706 (Fed. Cir. 1999). Extrinsic evidence may include, for example, treatises and expert testimony.

Patentees may limit claim scope by providing explicit definitions or by providing unequivocal guidance that dictates the manner in which the claims are to be construed. *See, e.g., SciMed Life Sys., Inc. v. Advanced Cardiovascular Sys., Inc.*, 242 F.3d 1337, 1344 (Fed. Cir. 2001). Thus, the specification may be used to determine if a patentee has limited the scope of the claim language by explicitly limiting statements made therein. *See, e.g., Watts v. XL Sys., Inc.*, 232 F.3d 877, 882 (Fed. Cir. 2000); *O.I. Corp. v. Tekmar Co.*, 115 F.3d 1576, 1581 (Fed. Cir. 1997); *Wang Lab., Inc. v. Am. Online, Inc.*, 197 F.3d 1377, 1382-83 (Fed. Cir. 1999).

Where the specification contains nothing to indicate that phrases are to be given anything other than their ordinary meanings, then those are the meanings the court must give them. *See, e.g., Vitronics*, 90 F.3d at 1582. Thus, a technical term used in a patent document is interpreted as having the meaning that it would be given by persons experienced in the field of the patent, unless it is apparent from the specification or the prosecution history that the patentee used the term with a different meaning. *See, e.g., CVI/Beta Ventures, Inc. v. Tura Lp*, 112 F.3d 1146, 1153 (Fed. Cir. 1997) (citation omitted) ("[i]t is always necessary to review the specification to determine whether the inventor has used any terms in a manner inconsistent with their ordinary meaning."). In addition, unambiguous claim language controls over alternative contradictory interpretations found in the specification. *See, e.g., Elekta Instrument S.A. v. UR Scientific Intl, Inc.*, 214 F.3d 1302, 1308 (Fed. Cir. 2000).

A court may also look to extrinsic evidence to assist in claim construction, which includes any evidence which is external to the patent and prosecution history, such as expert testimony, inventor testimony, dictionaries, technical treatises and articles. *Id.*; *Vitronics*, 90 F.3d at 1584. While extrinsic evidence may be useful in shedding light on the relevant prior art, a reviewing court is limited in relying on extrinsic evidence for claim interpretation purposes. *Phillips*, 415 F.3d at 1317-18. Thus, if the intrinsic evidence (specification, claims, and prosecution history) resolves any ambiguity in a disputed claim, extrinsic evidence cannot be used to contradict the established meaning of the claim language. *See, e.g., Mantech Envtl. Corp. v. Hudson Envtl. Servs.*, 152 F.3d 1368, 1373 (Fed. Cir. 1998); *Bell & Howell Document Mgmt. Prods. Co. v. Altek Sys.*, 132 F.3d 701, 706 (Fed. Cir. 1999). In addition, while use of expert testimony to explain an invention is admissible, courts may only rely upon extrinsic evidence to construe a claim term when the claim language remains genuinely ambiguous after consideration of the intrinsic evidence. *See, e.g., Phillips*, 415 F.3d at 1318; *Bell & Howell*, 132 F.3d at 706. Any expert testimony which is inconsistent with unambiguous intrinsic evidence, therefore, should be accorded no weight. *Phillips*, 415 F.3d at 1318.

3. Invalidity Analysis

Once the claims have been properly construed, in the case of an invalidity analysis, the second step requires the properly construed claims to be compared to the prior art reference(s) to determine whether the claim limitations are present in the prior art, either expressly or inherently. *See, e.g., Iron Grip Barbell Co., Inc. v. USA Sports, Inc.*, 392 F.3d 1317, 1323 (Fed. Cir. 2004); *In re Schreiber*, 128 F.3d 1473, 1477 (Fed. Cir. 1997). Whether a limitation is present in a prior art reference is a factual determination and thus may be submitted to a jury if the case is not tried to the court. *See Rapoport*, 254 F.3d at 1060. However, whether a claim is obvious in view of the prior art is a question of law that is subject to underlying factual determinations. *Id.* at 1057-58.

The disclosure of the specification must also be examined with respect to each construed claim to determine if it meets the legal standards for written description. *University of Rochester v. G.D. Searle & Co., Inc.*, 358 F.3d 916, 921 (Fed. Cir. 2004).

4. Obviousness Under 35 U.S.C. § 103

Under 35 U.S.C. § 103, an applicant is not entitled to a patent "if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains." The Supreme Court set the standard for obviousness in *Graham v. John Deere*, 383 U.S. 1 (1966), identifying the factual inquiries for determining obviousness. The relevant factual inquiries include:

(a) determining the scope and contents of the prior art;

(b) ascertaining the differences between the prior art and the claims in issue;

(c) resolving the level of ordinary skill in the pertinent art; and

(d) evaluating evidence of secondary considerations.

Id; see also Ruiz v. AB Chance Co., 234 F.3d 654, 663 (Fed. Cir. 2000). The Supreme Court reiterated the applicability of the *Graham* factors in *KSR Co. v. Teleflex Inc.*, 550 U.S. 398 (2007).

To establish *a prima facie* case of obviousness, three basic criteria must be met. First, there must be some reason to modify or combine the prior art references. *See, e.g., Takeda Chem. Indus. Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007). This motivation need not come from the references themselves nor must it be explicitly stated, but may reside in the knowledge generally known to one of ordinary skill in the art. *Id.* at 1357 (citing *KSR*, 550 U.S. at 401). For chemical compounds, *a prima facie* case of obviousness further requires "structural similarity between claimed and prior art subject matter...where the prior art gives reason or motivation to make the claimed compositions." *In re Mayne*, 104 F.3d 1339, 1342 (Fed. Cir. 1997) (citation omitted).

Second, there must be a reasonable expectation of success. *See, e.g., PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1360 (Fed. Cir. 2007) (citing *KSR*, 550 U.S. at 417). This expectation, however, need not be guaranteed or amount to absolute predictability. *In re O'Farrell*, 853 F.2d 894, 903-904 (Fed. Cir. 1988) (citation omitted).

Third, the prior art reference (or references when combined), or the combination of the prior art references with the knowledge of an ordinary artisan, must teach or suggest all the claim limitations. *See, e.g., Dann v. Johnston*, 425 U.S. 219, 230 (1976).

In the *KSR* case, the Supreme Court rejected the Federal Circuit's rigid rule of requiring that there be an explicit teaching, suggestion, or motivation to combine references to make the claimed invention. 550 U.S. at 415. Instead, the Court found that other factors, including the availability of design or market pressures, may provide the motivation to make the claimed

invention. "When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue" known options available to make the claimed invention. *Id.* at 421. The Court in *KSR* also held that if a combination or improvement is no more than a predictable use of prior art elements, that combination would have been obvious to one of ordinary skill in the art. *Id.* at 416. The Court recognized the creativity of an ordinary practitioner, and that a skilled artisan may "be able to fit the teachings of multiple patents together like pieces of a puzzle." *Id.* at 420. "A person of ordinary skill is also a person of ordinary creativity, not an automaton." *Id.* at 421.

Accordingly, simple substitution of known elements for another, or use of known techniques to improve a method in a similar way, such that the substitution or techniques are "obvious to try" to one of ordinary skill in the art, may form the basis of establishing obviousness. *Id.*

a) Level of Ordinary Skill in the Art

The hypothetical person of ordinary skill in the art is not an extraordinarily innovative person, nor a researcher of inexhaustible patience, but is a person who thinks conventionally in matters affecting the art in which he or she is skilled. *Standard Oil Co. v. Am. Cyanamid Co.*, 774 F.2d 448, 454 (Fed. Cir. 1985). "Ordinary skill means at least the ability to understand the technology and make modest adaptations or advances." *See In re Mahurkar Patent Litig.*, 831 F. Supp. 1354, 1374 (N.D. Ill. 1993), *aff'd* 71 F.2d 1573 (Fed. Cir. 1995). Factors that may be considered for determining the level of a skilled practitioner include: the educational level of the inventor; types of problems encountered in the art; prior art solutions to these problems; rapidity with which innovations are made; sophistication of the technology; and educational level of active workers in the field. *Daiichi Sankyo, Ltd. v. Apotex, Inc.*, 501 F.3d 1254, 1256 (Fed. Cir. 2007) (citation omitted). The hypothetical person of ordinary skill in the art is assumed to be aware of all pertinent prior art. *See, e.g., Standard Oil Co.*, 774 F.2d at 454.

b) Scope and Content of the Prior Art

As an initial inquiry under *Graham*, the scope and content of the prior art must be considered. *See, e.g., Eolas Techs. Inc. v. Microsoft Corp.*, 399 F.3d 1325, 1335 (Fed. Cir. 2005) (citation omitted); *see also* MPEP § 2144.08. A prior art reference is relevant if it is reasonably pertinent to the problem being addressed. *See In re ICON Health and Fitness, Inc.*, 496 F.3d 1374, 1379-80 (Fed. Cir. 2007). "'A reference is reasonably pertinent if, even though it may be in a different field from that of the inventor's endeavor, it is one which, because of the matter with which it deals, logically would have commended itself to an inventor's attention in considering his problem.'" *Id.* (quoting *In re Clay*, 966 F.2d 656, 659 (Fed. Cir. 1992)). A party's admissions may also create valid prior art. *See, e.g., In re Fout*, 675 F.2d 297, 300 (C.C.P.A. 1982) (citation omitted).

Furthermore, in determining obviousness, both prior art references and general knowledge in the art can be considered. *See, e.g., Leapfrog Enterprise Inc. v. Fisher-Price Inc.*, 485 F.3d 1157, 1161 (Fed. Cir. 2007) ("We agree with Fisher-Price that the district court correctly concluded that the subject matter of claim 25 of the '861 patent would have been

obvious in view of the combination of Bevan, the SSR, and the knowledge of one of ordinary skill in the art. An obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not.") *See KSR*, 550 U.S. at 420-21.

c) Differences between the Prior Art and the Claimed Invention

The differences between the prior art and the scope of the claimed invention must also be ascertained to determine those aspects of the claimed subject matter that may be obvious or nonobvious against the prior art and the knowledge of a skilled artisan. *Graham*, 383 U.S. at 22-23; *see also Dystar Textilfarben GmbH & Co. v. Deutschland KG v. C.H. Patrick Co.*, 464 F.3d 1356, 1369 (Fed. Cir. 2006). In *Graham*, the Supreme Court found patentee's plastic sprayer with a "hold-down" lid serving as obvious, holding that the differences from the claimed subject matter to the prior art were "exceedingly small and quite nontechnical" and that the device was "old in the art." *Graham*, 383 U.S. at 36-37. Accordingly, the degree of differences between the prior art and the claimed invention may be useful to a reviewing court in determining whether an invention is obvious.

5. Obviousness of Structurally Similar Compounds

The Federal Circuit has opined that the case law concerning *prima facie* obviousness for structurally similar compounds is "well-established." *Takeda*, 492 F.3d at 1356. In *Takeda*, the court stated that *a prima facie* case of obviousness is created by "structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions..." *Id. (quoting In re Dillon*, 919 F.2d 688, 692 (Fed. Cir. 1990) (en banc)). In addition, "a *prima facie* case of obviousness further requires a showing of 'adequate support in the prior art' for the change in structure." *Id. (quoting In re Grabiak*, 769 F.2d 729, 731-32 (Fed. Cir. 1985)). The prior art must also provide "a reasonable expectation of success, [but] not absolute predictability." *Eli Lilly and Co. v. Zenith Goldline Pharma, Inc.*, 471 F.3d 1369, 1377 (2006) (quoting *In re Longi*, 759 F.2d 887, 896 (Fed. Cir. 1985)).

Thus, a party asserting invalidity of a chemical compound can establish a *prima facie* case of obviousness by identifying: (1) a prior art compound having structural similarity to the claimed compound; and (2) reason or motivation in the prior art to modify the compound as necessary to obtain the claimed compound. As explained by the *Takeda* court, "in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular matter to establish *prima facie* obviousness of a new claimed compound." *Takeda*, 492 F.3d at 1357. Such reason or motivation need not be explicit "in the prior art references sought to be combined, but rather 'may be found in any number of sources, including common knowledge, the prior art as a whole, or the nature of the problem itself.'" *Pfizer, Inc. v.*

Apotex, Inc., 480 F.3d 1348, 1362 (Fed. Cir. 2007) (quoting *DyStar Textilfarben GmbH v. C.H. Patrick, Co.*, 464 F.3d 1356, 1361 (Fed. Cir. 2006)).[3]

a) Lead Compound

A lead compound is a prior art compound that is structurally similar to the claimed subject matter. Such a compound provides a starting point for an obviousness inquiry. *See Eisai Co. Ltd. v. Dr. Reddy's Laboratories, Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008) ("In other words, post-KSR, *a prima facie* case of obviousness for a chemical compound still, in general, begins with the reasoned identification of a lead compound"). The Federal Circuit stated that "[n]ormally a *prima facie* case of obviousness is based upon structural similarity, *i.e.*, an established structural relationship between a prior art compound [*i.e.*, a lead compound] and the claimed compound." *Takeda*, 492 F.3d at 1356 (quoting *In re Deuel*, 51 F.3d 1552, 1558 (Fed. Cir. 1995)). Such structural similarities "may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds." *Id.* (quoting *Deuel*, 51 F.3d at 1558).[4]

b) Structural Modifications

In the context of structurally similar compounds, "mere identification in the prior art of each component of a composition does not show that the combination as a whole" is obvious. *Eli Lilly*, 471 F.3d at 1379 (citing *Yamanouchi Pharm. Co., Ltd v. Danbury Pharmacal, Inc.*, 231 F.3d 1339 (Fed. Cir. 2000)); *In re Kahn*, 441 F.3d 977, 986 (Fed. Cir. 2006) (citing *In re Rouffet*, 149 F.3d 1350, 1355 (Fed. Cir. 1998)). Rather, *prima facie* obviousness requires a showing that the "prior art would have suggested making the specific molecular modifications [to that lead compound] necessary to achieve the claimed invention." *Takeda*, 492 F.3d at 1356 (quoting *Deuel*, 51 F.3d at 1558); *see also Eisai*, 533 F.3d at 1357 ("Obviousness based on structural similarity thus can be proved by identification of some motivation that would have led one of ordinary skill in the art to select and then modify a known compound (*i.e.*, a lead compound) in a particular way to achieve the claimed compound").

In *Pfizer*, the Federal Circuit held that a modified form of a compound was obvious where motivation to make the necessary modifications was found in the art. 480 F.3d at 1352-53.

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[3] The Federal Circuit further held that these requirements are consistent with the legal principles promulgated by the Supreme Court in *KSR*. *Takeda*, 492 F.3d at 1356 (explaining that the "*KSR* Court rejected a rigid application of the [Federal Circuit's] teaching, suggestion or motivation ('TSM') test" but "acknowledged the importance of identifying 'a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does"); *see also In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007).

[4] For example, "[a] known compound 'may suggest its homolog, analog, or isomer because such compounds 'often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties.'" *Takeda*, 492 F.3d at 1356 (quoting *Deuel*, 51 F.3d at 1558).

The claims at issue disclosed the besylate salt form of a previously known drug compound. *Id.* at 1354. The besylate form possessed a number of advantages over alternate acid addition salts of the drug, including improved drug stability, solubility, and non-stickiness that facilitated commercial processing. *Id.* at 1357. However, the efficacy of the besylate form remained unaltered compared to prior art salt forms. *Id.* at 1355.

The defendants alleged that the besylate salt form was obvious where besylate salts of approved drugs were known in the art at the time of invention. *Id.* at 1356. The Federal Circuit agreed, stating the evidence "easily satisfies us" that the formulation was obvious. *Id.* at 1361. First, the court found motivation to choose salts that differed from prior art salts exhibiting stability and stickiness problems. *Id.* at 1362. Moreover, the Federal Circuit held that an analysis of the physiological effect and solubility of a drug is important in determining motivation for modifying compounds in the prior art. *See, e.g., Id.* at 1364.[5] Next, the court discounted the patentee's argument—that only one in 400 approved drugs cited in the prior art used the besylate form—because only 53 anions were approved by the FDA at the time of application and one of skill would choose from among those 53. *Id.* at 1363. Finally, the court found motivation to modify the drug in prior art references that described the benefits of besylate, including improved drug stability. *Id.*

The court was not persuaded by the patentee's argument that the effects of a particular salt could only be ascertained by experimentation, because the expectation of success need only be reasonable, not absolute, and the besylate form was known to work with previously approved drugs. *Id.* at 1364. The court found that the patentee's testing of various salts was "nothing more than routine application of a well-known problem-solving strategy" and "the work of a skilled [artisan], not of an inventor." *Id.* at 1368 (internal quotations and citations omitted).

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[5] "But the outcome of this case need not rest heavily on the size of the genus of pharmaceutically-acceptable anions disclosed by Berge because clear and convincing evidence establishes that, out of the list of 53 anions, one of ordinary skill in the art would have favorably considered benzene sulphonate because of its known acid strength, *solubility*, and *other known chemical characteristics* as reported in several other publications Pfizer has admitted are prior art. Schmidt discloses that aryl sulphonic acids, such as benzene sulphonic acids, considerably increase the *solubility* of pharmaceuticals containing one or more basically reacting nitrogen atoms. Spiegel specifically identifies besylate as the preferred pharmaceutically-acceptable acid addition salt form of a pharmaceutical compound. Other patents not before the examiner during prosecution of the '303 patent also point to benzene sulphonate. U.S. Patent 3,970,662 to Carabateas (1976) ('Carabateas') discloses an intermediate dihydropyridine compound useful in the form of an acid addition salt derived from benzene sulphonate. U.S. Patent 4,432,987 to Barth (1984) ('Barth'), assigned to Pfizer, discloses the besylate acid addition salt form of a pharmaceutical composition having excellent *pharmacokinetic properties*, near-optimal *solubility*, and improved *stability*. Taken together, *these references provide ample motivation* to narrow the genus of 53 pharmaceutically-acceptable anions disclosed by Berge to a few, including benzene sulphonate." *Id.* at 1364 (emphasis added) (internal citations omitted).

c) Reasonable Expectation of Success

To support a *prima facie* case of obviousness for structurally similar compounds, the prior art must provide "a reasonable expectation of success, [but] not absolute predictability." *Eli Lilly and Co. v. Zenith Goldline Pharma, Inc.*, 471 F.3d 1369, 1377 (2006) (quoting *In re Longi*, 759 F.2d 887, 896 (Fed. Cir. 1985)). That the invention requires experimental verification of a predicted result does not make that result non-obvious. *Pfizer*, 480 F.3d at 1367 ("that [the patentee] had to verify through testing the expected traits of each [chemical modification] is of no consequence because it does not compel a conclusion of non-obviousness here"). Even resource intensive experimentation can be routine to one of skill in the art. *Id.* ("This is not to say that the length, expense, and difficulty of the techniques used are dispositive since many techniques that require extensive time, money, and effort to carry out may nevertheless be arguably 'routine' to one of ordinary skill in the art").

In *Pfizer*, the patentee tested various salt forms of a drug to determine which gave the best stability and processability. *Pfizer*, 480 F.3d at 1355-56. The patentee alleged that the chosen salt form was not obvious because its "'discovery'...was obtained through the use of trial and error procedures." *Id.* at 1366-67. Nevertheless the Federal Circuit found the resulting salt form obvious, "rel[ying] on the fact that one skilled in the art would have had a reasonable expectation of success at the time the invention was made, and merely had to verify that expectation." *Id.* at 1367.

d) Objective Indicia of Non-Obviousness

A patentee may rebut *a prima facie* case of obviousness through demonstration of any objective indicia (also known as secondary considerations) of nonobviousness. *See, e.g., In re Fielder*, 471 F.2d 640, 642-43 (C.C.P.A. 1973) (citations omitted). Such factors include: commercial success; long felt but unresolved need; licenses showing industry respect; copying; failure of others in the field; unexpected results; or skepticism of skilled artisans before the invention. *See also In re Rouffet*, 149 F.3d 1350, 1355 (Fed. Cir. 1998) (citing *Graham*, 383 U.S. at 17-18); *In re Mayne*, 104 F.3d 1339, 1342 (Fed. Cir. 1997). Any evidence, however, of secondary considerations must have a sufficient "nexus" with the claimed invention. *See, e.g., Stratoflex*, 713 F.2d at 1539 (no nexus between secondary considerations and the product of the patent at issue). The patentee ultimately bears this burden of demonstrating a nexus connection of secondary considerations with the claimed invention. *See, e.g., In re GPAC*, 57 F.3d 1573, 1580 (Fed. Cir. 1995).

6. Infringement Analysis

a) Direct Infringement

It is axiomatic that an invalid claim cannot be infringed. The burden is on the patentee to show infringement, literal or by equivalents. *See, e.g., Advanced Cardiovascular Sys., Inc. v. Scimed Life Sys., Inc.*, 261 F.3d. 1329, 1336 (Fed. Cir. 2001). The statutory definition of infringement is: "Except as otherwise provided in this title, whoever without authority makes, uses, offers to sell or sells any patented invention, within the United States or imports into the

United States any patented invention during the term of the patent therefore, infringes the patent." 35 U.S.C. § 271(a).

Determination of patent infringement is a two-step process. First, the court must construe the claims asserted to be infringed as a matter of law in order to establish their meaning and scope. *Markman v. Westview Instruments, Inc.*, 517 U.S. 370, 390-91 (1996) (*Markman II*). Second, the claims as construed are compared to the allegedly infringing device. An accused device may infringe a patent either literally or under the doctrine of equivalents. The Federal Circuit has adopted the "all limitations rule" for infringement, under which, to establish infringement of a patent, every limitation set forth in a claim must be found in an accused product or process exactly or by a substantial equivalent. *Corning Glass Works. v. Sumitomo Elec. U.S.A., Inc.*, 868 F.2d 1251 (Fed. Cir. 1989); *Laitram Corp v. Rexnord, Inc.*, 939 F.2d 1533 (Fed. Cir. 1991). The Supreme Court has specifically held that, in determining both literal infringement and infringement under the doctrine of equivalents, the focus must be on the individual claim elements rather than the invention as a whole. *Warner-Jenkinson Co., Inc. v. Hilton Davis Chemical Co.*, 520 U.S. 17 (1997).

To establish literal infringement, the accused device must be shown to embody every element of the claim under consideration. *Townsend Engineering Co.* v. *Hitec Co., Ltd.*, 829 F.2d 1086 (Fed. Cir. 1987). Alternatively, infringement under the doctrine of equivalents will be found if, and only if, the differences between the claimed and used products or processes are insubstantial. *Graver Tank and Mfg. Co.-v. Linde Air Products Co.*, 339 U.S. 605 (1950). In other words, the element substituted in the accused device for the element set forth in the claim must not substantially change the way in which the function of the claimed invention is performed. *Wolverine World Wide, Inc. v. Nike, Inc.*, 38 F.3d 1192 (Fed. Cir. 1994).

However, the patentee may not use the doctrine of equivalents to recover subject matter that has been surrendered in order to obtain the patent. Prosecution history estoppel may exclude as equivalents any subject matter that was, by amendment or argument during prosecution, relinquished. According to the Supreme Court, "a narrowing amendment made to satisfy any requirement of the Patent Act may give rise to an estoppel." *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 736, 62 USPQ2d 1705, 1711-12 (2002) (*Festo VIII*). In addition, a number of activities during prosecution, in addition to a narrowing amendment, may also give rise to prosecution history estoppel. *Haynes Int'l, Inc. v. Jessop Steel Co.*, 8 F.3d 1573, 1579 (Fed. Cir. 1998). Such activities include arguments made to obtain allowance of the claims at issue. *See Cybor Corp. v. FAS Techs., Inc.*, 138 F.3d 1448, 1460 (Fed. Cir. 1998) (*en banc*). To determine what subject matter has been relinquished, an objective test is applied, inquiring "whether a competitor would reasonably believe that the applicant had surrendered the relevant subject matter." *Cybor*, 138 F.3d at 1457.

B. U.S. Patent No. 8,927,606

1. Priority Information and Related Applications

U.S. Patent Number 8,927,606 ("the '606 patent") ("Exhibit 2") issued on January 6, 2015, from Application Serial Number 14/493,903 ("the '903 application"), filed on Sep. 23, 2014 as a divisional of Application Serial Number 14/261,720 (now U.S. Patent Number

8,871,813), filed Apr. 25, 2014, which is a divisional of Application Serial Number 14/165,976 (now U.S. Patent Number 8,754,131), filed on Jan. 28, 2014, which is a divisional of Application Serial Number 13/687,242 (now U.S. Patent Number 8,669,290), filed Nov. 28, 2012, which is a divisional of Serial No. 13/353,653 (now U.S. Patent Number 8,497,304), filed Jan. 19, 2012, which is a divisional of Serial No. 10/525,006 (now U.S. Pat. No. 8,129,431), filed Mar. 28, 2005, which is a national stage of International Application No. PCT/JP2004/000350 filed Jan. 16, 2004, which claims priority to a Japanese application filed January 21, 2003.

2. Claims of the '606 Patent

The thirty claims of the '606 patent are listed below:

1. A method for treating an inflammatory disease of an eye, the method comprising administering to said eye a stable aqueous liquid preparation that comprises: (a) a first component; and (b) a second component; wherein the first component is 2-amino-3-(4-bromobenzoyl) phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate; the first component is the sole pharmaceutical active ingredient contained in the preparation; the second component is tyloxapol and is present in said liquid preparation in an amount sufficient to stabilize said first component; wherein said stable liquid preparation is formulated for ophthalmic administration; and wherein said liquid preparation is administered to said eye at a dose and a frequency effective to treat said inflammatory disease.

2. The method according to claim 1, wherein said inflammatory disease is a disease of an anterior or posterior segment of said eye.

3. The method according to claim 2, wherein said disease is postoperative inflammation.

4. The method according to claim 1, wherein the first component is a 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt.

5. The method according to claim 1, wherein the concentration of tyloxapol is from about 0.01 w/v % to about 0.05 w/v %; and wherein the first component is a 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.01 to about 0.2 w/v %.

6. The method according to claim 5, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.02 w/v % to about 0.1 w/v %.

7. The method according to claim 5, wherein the aqueous liquid preparation further comprises a quaternary ammonium salt.

8. The method according to claim 5, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is about 0.1 w/v %.

9. The method according to claim 1, wherein the stable aqueous liquid preparation consists essentially of: (a) 2-amino-3-(4-bromobenzoyl) phenylacetic acid sodium salt, (d) sodium tetraborate, (e) EDTA sodium salt, (f) benzalkonium chloride, (g) polyvinylpyrrolidone, and (h) sodium sulfite, wherein said liquid preparation is formulated for ophthalmic administration, and wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.02 w/v % to about 0.1 w/v %.

10. The method according to claim 1, wherein said dose comprises one or two drops.

11. A method for treating an inflammatory disease of an eye, the method comprising administering to said eye a stable aqueous liquid preparation that comprises: (a) a first component; and (b) a second component; wherein the first component is 2-amino-3-(4-bromobenzoyl) phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate; the first component is the sole pharmaceutical active ingredient contained in the preparation; the second component is tyloxapol; wherein said stable liquid preparation is formulated for ophthalmic administration; 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; and wherein said liquid preparation is administered to said eye at a dose and a frequency effective to treat said inflammatory disease.

12. The method according to claim 11, wherein the stable aqueous liquid preparation is characterized in that greater than about 92% of the original amount of the first component remains in the preparation after storage at about 60° C. for 4 weeks.

13. The method according to claim 11, wherein said inflammatory disease is a disease of an anterior or posterior segment of said eye.

14. The method according to claim 13, wherein said disease is postoperative inflammation.

15. The method according to claim 11, wherein the concentration of tyloxapol is from about 0.01 w/v % to about 0.05 w/v %; and wherein the first component is a 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.01 to about 0.2 w/v %.

16. The method according to claim 15, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.02 w/v % to about 0.1 w/v %.

17. The method according to claim 11, further comprising a quaternary ammonium salt.

18. The method according to claim 11, wherein the stable aqueous liquid preparation consists essentially of: (a) 2-amino-3-(4-bromobenzoyl) phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate; (b) tyloxapol; (c) boric acid; (d) sodium tetraborate; (e) EDTA sodium salt; (f) benzalkonium chloride; (g) polyvinylpyrrolidone; and (h) sodium sulfite; and wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.02 w/v % to about 0.1 w/v %.

19. A method for treating an inflammatory disease of an eye, the method comprising administering to said eye a stable aqueous liquid preparation that comprises: (a) a first component; and (b) a second component; wherein the first component is 2-amino-3-(4-bromobenzoyl) phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate; the first component is the sole pharmaceutical active ingredient contained in the preparation; the second component is tyloxapol; wherein said stable liquid preparation is formulated for ophthalmic administration; provided that the liquid preparation does not include mannitol; and wherein said liquid preparation is administered to said eye at a dose and a frequency effective to treat said inflammatory disease.

20. The method according to claim 19, wherein said inflammatory disease is a disease of an anterior or posterior segment of said eye.

21. The method according to claim 20, wherein said disease is postoperative inflammation.

22. The method according to claim 19, wherein the first component is a 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt.

23. The method according to claim 22, wherein the concentration of tyloxapol is from about 0.01 w/v % to about 0.05 w/v % and the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.05 to about 0.2 w/v %.

24. The method according to claim 22, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.02 w/v % to about 0.1 w/v %.

25. The method according to claim 20; wherein the stable aqueous liquid preparation consists essentially of: (a) 2-amino-3-(4-bromobenzoyl) phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate; (b) tyloxapol; (c) boric acid; (d) sodium tetraborate; (e) EDTA sodium salt; (f) benzalkonium chloride; (g) polyvinylpyrrolidone; and (h) sodium sulfite; wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.02 w/v % to about 0.1 w/v %.

26. The method according to claim 20, 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.

27. The method according to claim 20, wherein the concentration of tyloxapol is from about 0.01 w/v % to about 0.05 w/v %; and wherein the first component is a 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.02 to about 0.1 w/v %.

28. The method according to claim 1, wherein the aqueous liquid preparation further satisfies the preservative efficacy standard of EP-criteria B of the European Pharmacopoeia as follows: viable cell counts of bacteria (*S. aureus*, *P. aeruginosa*) 24 hours and 7 days after inoculation decrease to not more than 1/10 and not more than 1/1000, respectively, and thereafter, the cell count levels off or decreases; and viable cell count of fungi (*C. albicans*, *A. niger*) 14 days after inoculation decreases to not more than 1/10, and thereafter, the cell count keeps the same level as that of 14 days after inoculation.

29. The method according to claim 11, wherein the aqueous liquid preparation further satisfies the preservative efficacy standard of EP-criteria B of the European Pharmacopoeia as follows: viable cell counts of bacteria (*S. aureus*, *P. aeruginosa*) 24 hours and 7 days after inoculation decrease to not more than 1/10 and not more than 1/1000, respectively, and thereafter, the cell count levels off or decreases; and viable cell count of fungi (*C. albicans*, *A. niger*) 14 days after inoculation decreases to not more than 1/10, and thereafter, the cell count keeps the same level as that of 14 days after inoculation.

30. The method according to claim 19, wherein the aqueous liquid preparation further satisfies the preservative efficacy standard of EP-criteria B of the European Pharmacopoeia as follows: viable cell counts of bacteria (*S. aureus*, *P. aeruginosa*) 24 hours and 7 days after inoculation decrease to not more than 1/10 and not more than 1/1000, respectively, and thereafter, the cell count levels off or decreases; and viable cell count of fungi (*C. albicans*, *A. niger*) 14 days after inoculation decreases to not more than 1/10, and thereafter, the cell count keeps

the same level as that of 14 days after inoculation.

3. Specification of the '606 Patent

The specification of the '606 patent defines the invention as "an aqueous liquid preparation containing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof and an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester." *'606 patent, col. 1, ll. 6-15.* The specification further recites that "[i]t is an object of the present invention to provide an aqueous liquid preparation comprising 2-amino-3-(4-bromobenzoyl)phenylacetic acid…in which, when a preservative such as benzalkonium chloride is incorporated therein, preservative effect of the preservative does not substantially deteriorate." *Id., col. 2, ll. 7-14.*

The specification defines tyloxapol as an alkyl aryl polyether alcohol type polymer. *Id., Abstract.*

The specification describes benzalkonium chloride as a quaternary ammonium compound having a preservative effect. *Id., col. 2, ll. 23-29.*

The specification teaches that the stability of sodium 2-amino-3-(4-bromobenzoyl)phenylacetate in an eye drop formulation is greatest in a tyloxapol-containing preparation and poorest in a polysorbate 80-containing preparation. *Id., col. 7, ll. 10-22.* The stability of a polyoxyl 40 stearate-containing preparation is intermediate between that of a tyloxapol-containing preparation and a polysorbate 80-containing preparation. *Id.* Also, eye drops containing sodium 2-amino-3-(4-bromobenzoyl)phenylacetate and tyloxapol are more stable when 0.02 w/v % of tyloxapol is present in the formulation than when 0.15 w/v % of tyloxapol is present in the formulation. *Id.*

4. Prosecution Histories

a) Prosecution History of The '606 Patent

The prosecution history of the '606 patent is attached as Exhibit 3. The '606 patent was filed as Application Serial Number 14/493,903 ("the '903 application"). The '903 application was filed with 18 claims, all canceled by preliminary amendment.

i) Preliminary Amendment

Claims 1-18 as filed were canceled in a preliminary amendment filed on September 23, 2014, in favor of new claims 19-48. *Prosecution History of the '606 patent*; Preliminary Amendment dated September 23, 2014. Claims 19-48 matured into claims 1-30 without substantial amendment, and were only renumbered. Therefore, claims 19-48 are not reproduced below.

ii) Terminal Disclaimers dated November 5, 2014

The Applicants filed terminal disclaimers over multiple family members including the '813 patent, the '131 patent, the '290 patent, the '304 patent, and the '431 patent. *Id.*; Terminal Disclaimers filed November 5, 2014.

iii) Notice of Allowance

A Notice of Allowance was issued on November 19, 2014. *Id.*, Notice of Allowance.

b) Prosecution History of The '431 Patent

U.S. Patent Number 8,129,431 ("the '431 patent") is related to the '606 patent and the '431 patent's file history is attached as Exhibit 4. The file history is summarized below. The '431 patent was filed as Application Serial Number 10/525,006 ("the '006 application"), filed as a U.S. National Stage Application based on International Application PCT/JP2004/000350, filed on January 16, 2004. The '006 application entered the National Stage on February 17, 2005. The '006 application was filed with 18 claims.

i) Preliminary Amendments

Claims 1–18 as filed were canceled in a preliminary amendment filed on March 20, 2007, in favor of new claims 19–40 presented in a preliminary amendment filed on March 20, 2007, and amended on April 3, 2007. *Prosecution History of the '431 patent*; Preliminary Amendments dated March 20, 2007 and April 3, 2007. Claim 19, as amended on April 3, 2007, is presented below:[6]

> 19. (Previously presented) An aqueous liquid preparation comprising 2-amino-3-(4bromobenzoyl) phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester.

Id. Dependent claims recited such features as tyloxapol concentration, bromfenac concentration, and use of bromfenac sodium. *Id.* claims 20-24.

ii) Office Action dated September 27, 2007

In an Office Action dated September 27, 2007, the Examiner rejected claim 19 under 35 U.S.C. § 102(b) as being anticipated by Gamache et al. (WO 01/15677 A2). *Id.*, Office Action dated September 27, 2007. The Examiner alleged that:

> Gamache teaches all of the components of the claims: compositions for otic and intranasal use…that contain a combination of a 5-HT agonist and an antiinflammatory agent…; specifically claimed is the anti-inflammatory specie

[6] For the sake of brevity, the following discussion focuses on independent claims filed during prosecution of the '006 application.

bromfenac...; tyloxapol is taught at the concentration of 0.05 % (w/v) (p. 16, line 30).

Id.

Claim 19 was also rejected under 35 U.S.C. § 102(b) as being anticipated by Dobrozsi (US 6,319,513). *Id.* According to the Examiner, "Dobrozsi teaches aqueous liquid compositions comprising a pharmaceutically active agent selected from a group that includes analgesics...; a specie taught is bromfenac (column 10, line 11); tyloxapol is taught at 0.15 and 0.035 %...." *Id.*

Claims 19-24 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Gamache and ISTA Pharmaceuticals ("New Drug Applications: Xibrom", http://www.drugs.com/nda/xibrom040525.html) or Nolan, *et al.* (Agents and Actions; 1988 Aug; 25(1-2):77-85, abstract). *Id.* The Examiner alleged that Gamache "does not specifically teach the sodium salt of bromfenac, nor a hydrate, nor the concentration range or specific bromfenac sodium concentrations..., nor the tyloxapol concentrations." *Id.*

The Examiner relied upon the ISTA Pharmaceuticals news release and Nolan to show products containing 0.1-0.32 % bromfenac sodium were known. "It would have been obvious for one of ordinary skill in the art at the time of the invention to select concentrations of bromfenac sodium... of 0.1, about 0.2 and about 0.32 % in the invention of Gamache, since these values have demonstrated efficacy for topical use." *Id.*

The Examiner further stated that "[i]t would have been obvious to adjust the concentration of tyloxapol, to see what the effect would be on the solubility and stability.... It would also have been obvious to adjust the pH to values in the 7.5 to 8.5 range, with the potential of dissolving and/or stabilizing more of the acidic drug, bromfenac..." *Id.*

Claims 19-24 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Yakuji Nippo Ltd. ("New Drugs in Japan"; 2001) and Xia (US 6,369,112). *Id.* The Examiner stated that Yakuji Nippo taught "a bromfenac sodium sesquihydrate ophthalmic formulation that contains: 0.1% (w/v) bromfenac (items 1-3); boric acid buffer, sodium sulfite, disodium edetate, polyvinylpyrrolidone, and benzalkonium chloride (item 2, additives); a pH of 8.0-8.6 (item 2, pH)." *Id.* The Examiner alleged that Yakuji Nippo did not teach tyloxapol. *Id.* However, the Examiner relied upon Xia to teach that tyloxapol at concentrations of 0.25 and 0.025% "improves the stability and therefore the disinfecting efficacy over time of an active component" in a solution for cleaning contact lenses. *Id.* The Examiner alleged that it would have been obvious to stabilize the active ingredient in the ophthalmic formulation Yakuji Nippo using tyloxapol. *Id.* "There would have been an expectation of success, since tyloxapol has demonstrated efficacy with the contact lens cleaning solutions." *Id.*

Claims 19-24 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Yakuji Nippo and Xia (US 6,369,112 B1) as applied to claims 19-30, and further in view of Nolan. *Id.* The Examiner alleged that "[n]either Yakuji Nippo or Xia teach the bromfenac sodium hydrate solutions at a bromfenac concentration of 0.2 %;" but relies upon Nolan to show that topical solutions are "efficacious in the concentration range of 0.1-0.32 %." *Id.*

iii) Response dated March 26, 2008

A response dated March 26, 2008, was filed after an Examiner's Interview held on March 13, 2008.[7] *Id.*, Response dated March 26, 2008. In their response, the Applicants amended claim 19 as follows:

> 19. (Currently amended) An aqueous liquid preparation comprising at least the following two components. the first component comprising 2-amino-3-(4bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and the second component comprising an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester.

Id.

The Applicants additionally introduced new independent claims 41 and 63, reproduced below:

> 41. (New) An aqueous liquid preparation consisting essentially of at least the following two components, the first component comprising 2-amino-3-(4bromobenzoyl) phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and the second component comprising an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester.
>
> 63. (New) An aqueous liquid preparation consisting of the following two components, the first component comprising 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and the second component comprising an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester, and optionally at least one preservative, isotonic, buffer, thickener, stabilizer, chelating agent, pH controlling agent, or perfume.

Id.

In the Response, the Applicants expressly alleged that "[t]he subject matter of the present invention is directed to the specific combination of 2-amino-3-(4- bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof and an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester." *Id.*

[7] While an Interview Summary Form is present in the file history, details of the discussion are not provided. However, the Applicant's summary of the Interview provided the details reiled up herein.

The Applicants summarized the Examiner's Interview as follows:

> Claim 19 has been amended as suggested by the Examiners to clarify that the claimed preparation has at least two components, the first component and the second component as described above.
>
> * * *
>
> New claims 41–63 have been added for additional patent protection. Claims 41–62 correspond to claims 19–40, respectively, except in reciting that the preparation "consists essentially of" the recited components. New claim 63 corresponds to claim 19, except that the claim recites "consisting of" the recited components....

Id.

The Applicants alleged that Gamache, cited by the Examiner, did not disclose "this specific combination" of bromfenac and an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester. *Id.* The Applicant alleged that Gamache was directed to compositions comprising 5-HT_{1D} and/or HT_{1B} agonists, and cited bromfenac only as one of many possible anti-inflammatory additives. *Id.* Further,

> although tyloxapol (0.05% w/v) is added to an IB/ID agonist (0.1-1.0% w/v) and moxifloxacin (0.3% w/v) in Example 4 [of Gamache]..., there is no explanation about tyloxapol in the description of Gamache et al. or why it is included. Moreover in this Example, moxifloxacin...is not an anti-inflammatory agent like bromfenac. Thus it is unclear from Gamache et al. why tyloxapol is added to the otic/nasal suspension containing IB/ID agonist and moxifloxacin.
>
> "Tyloxapol" described in Example 4 is just a single word description and does not give any clues and hints to the present invention. Therefore, the word "tyloxapol" described only in Example 4 does not destroy the novelty of the present invention.

Id.

The Applicants alleged that Dobrozsi did not anticipate claim 19, as it neither "describes nor suggests the specific combination of 2-amino-3(4- bromobenzoyl)phenylacetic acid...and an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester..."

> Although tyloxapol is added to oxymethazoline hydrochloride in the preparation of mucoretentive intranasal spray decongestant (Example 10)...in Dobrozsi, no explanation about tyloxapol is given.
>
> Besides, oxymethazoline hydrochloride is a well known adrenergic, and is not an antiinflammatory agent like bromfenac.

Id.

ii) Level of Ordinary Skill in the Art

The level of ordinary skill in the art is discussed above and is, therefore, not repeated here.

iii) Differences Between the Art and the Claims

As discussed *supra*, the formulation of Example 6 of the '225 patent differs from the formulation used in the method of claim 1 in that it contains the nonionic surfactant polysorbate 80 rather than the nonionic surfactant tyloxapol. The preparation is used to treat inflammatory conditions and is administered ophthalmically.

Also discussed above, the '343 patent describes a specific example (Example 2) of an aqueous preparation of eye drops comprising diclofenac benzalkonium chloride and the non-ionic surfactant, tyloxapol for the treatment of inflammatory conditions:

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

'343 patent.,col. 8, ll. 1-15. The '343 patent, therefore, provides the missing non-ionic surfactant tyloxapol in an aqueous liquid opthalmic formulation of another NSAID (diclofenac potassium).

iv) Motivation to Combine the References

A person of ordinary skill in the art would have had reason to combine the '225 and '343 patents to arrive at the formulation recited in claim 1 as it was known prior to the '606 Patent that acidic NSAIDs (such as bromfenac) containing an ionizable carboxylic acid group form complexes with quaternary ammonium preservatives, such as BAC in ophthalmic formulations. The interaction of the NSAID with BAC results in complexes that were known to precipitate out of the ophthalmic formulation, which is problematic because it (1) renders the preservative (e.g., BAC) less available to serve its function and (2) reduces the availability of the NSAID (e.g., bromfenac).

The prior art also described ophthalmic formulations of acidic NSAIDs containing a non-ionic surfactant like tyloxapol.

Both the '225 and '343 patents relate to ophthalmic formulations of acidic NSAIDs containing BAC and a nonionic surfactant. Specifically, the '225 patent teaches stable ophthalmic formulations containing bromfenac (an acidic NSAID), BAC, and polysorbate 80 (a non-ionic surfactant), and the '343 patent teaches that tyloxapol (another non-ionic surfactant) was the preferred surfactant for use in aqueous ophthalmic preparations of diclofenac (another acidic NSAID) and BAC. A person of ordinary skill in the art would have known that substituting polysorbate 80 with tyloxapol would successfully, and predictably, result in a stable ophthalmic formulation of bromfenac and BAC because tyloxapol and polysorbate 80 had previously been used interchangeably as surfactants in ophthalmic formulations. The '225 patent teaches that the aqueous liquid bromfenac preparations formulated with polysorbate 80 will be useful for ophthalmic administration.

In addition it was also known that tyloxapol was a preferred or better solubilizer than polysorbate 80 for acidic compounds in aqueous ophthalmic formulations. The '343 patent teaches that tyloxapol is a preferred solubilizer. *'343 patent*, col. 4, l. 62. The '609 patent further provides motivation to use tyloxapol over polysorbate. Specifically, the '609 patent teaches that tyloxapol is superior to polysorbate 80 in solubilizing acidic ophthalmic drugs:

TABLE 4

	Formulation					
Component	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 dihydrogen 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

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

'609 Patent, col. 6, l. 65 – col. 7, l. 34.

According to the '609 patent, solutions with tyloxapol (A and B) had the greatest residual rate of pranlukasut while solutions with polysorbate 80 (D-E) had lower residual rates.

A person of ordinary skill in the art would have had motivation to substitute, and a reasonable expectation of success in substituting, tyloxapol for polysorbate 80, because the '225 patent provides working examples of bromfenac preparations formulated with polysorbate 80 and the '609 patent teaches that tyloxapol is superior to polysorbate 80 in solubilizing acidic ophthalmic drugs. *'609 patent,* col 10, ll. 5-18.

Accordingly, a person of ordinary skill in the art would have had motivation to substitute, and a reasonable expectation of success in substituting, tyloxapol for polysorbate 80, because the prior art such as the '343 patent provides an example of stable aqueous preparations containing NSAIDs (similar to bromfenac) formulated with BAC and tyloxapol (and other closely related non-ionic surfactants). Further, a person of ordinary skill would have had motivation to prepare a bromfenac ophthalmic formulation containing tyloxapol as the surfactant because tyloxapol was the best solubilizing agent used to stabilize an ophthalmic pranlukasut formulation according to the '609 patent. "[W]hen a patent 'simply arranges old elements with each performing the same

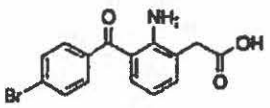
function it had been known to perform' and yields no more than one would expect from such an arrangement, the combination is obvious." *KSR*, 550 U.S. at 416 (citing *Sakraida v. AG Pro, Inc.*, 425 U.S. 273 (1976)).

Since a person of ordinary skill in the art would have been motivated in view of the '343 and '609 patents, to replace polysorbate 80 with tyloxapol, the combination of the prior art teaches all of the elements of claim 1, and claim 1 is *prima facie* obvious over the prior art.

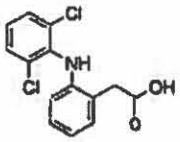
As an alternative to switching nonionic surfactants in the aqueous ophthalmic preparations of the '225 and '343 patents, it would have also been obvious to switch NSAIDs. Thus, it would have been obvious to use bromfenac from the '225 patent's Example 6 instead of diclofenac in the '343 patent's Example 2.

As discussed *supra*, Example 2 in the '343 patent describes an ophthalmic formulation containing diclofenac (an acidic NSAID), BAC, and tyloxapol. The only difference between the ophthalmic formulation of Example 2 in the '343 patent and the ophthalmic preparation recited in claim 1 is that the acidic NSAID in the '343 patent's example is diclofenac potassium, whereas the acidic NSAID in claim 1 is bromfenac.

Bromfenac and diclofenac are both NSAIDs sharing several structural features, as depicted below:



Bromfenac



Diclofenac

Hara describes bromfenac as superior to diclofenac and provides a person of ordinary skill in the art a reason to substitute the diclofenac in the '343 patent's Example 2 with the bromfenac in the '225 patent's Example 6. Hara also describes "[b]romfenac sodium hydrate [as] a type of NSAID that was developed in order to address the needs of clinical sites, and it is indicated for use in a broad range of [ophthalmic] conditions, from inflammation of the outer ocular area to post-operative inflammation of the anterior ocular segment." *Hara*, 1014:1:2. Hara compared bromfenac with three other NSAIDs that existed in the prior art—pranoprofen, indomethacin, and diclofenac sodium. *Hara*, 1014:2:2-1014:2:5. Hara concluded that bromfenac "shows superior efficacy in treating anterior eye inflammation and post-operative inflammation." *Hara*, 1015:2:2.

A person of ordinary skill in the art, familiar with the '343 and '225 patents, would have had a reason to combine their teachings because the '343 patent teaches an aqueous liquid ophthalmic formulation of diclofenac formulated with tyloxapol and benzalkonium chloride, and Hara teaches that bromfenac [sodium hydrate] as disclosed in the '225 patent, is broadly applicable for treatment of various ophthalmic conditions, and preferable as compared to diclofenac. Thus, a person of ordinary skill in the art, reading '343 and '225 patents, would have

had a reason to substitute the bromfenac of '225 patent's Example 6 for diclofenac in '343 patent's Example 2.

A person of ordinary skill in the art would have known that substituting bromfenac for diclofenac would have yielded predictable results because both are NSAIDs with similar pharmacological properties. Furthermore, a person of ordinary skill in the art facing a design need to formulate a stable bromfenac solution would have found it at least obvious to try to prepare an aqueous liquid bromfenac preparation comprising tyloxapol because Hara teaches that there were only four NSAID ophthalmic drugs available on the market by 2003, "resulting in limited choices." Hara, 1014:2:2. Therefore, in view of the '343 and '225 patents, and in further view of Hara, a person of ordinary skill would have reasonably expected to be able to make and use an aqueous liquid ophthalmic preparation within the scope used in claim 1 of the '606 patent and accordingly, claim 1 is invalid.

f) Secondary Considerations

In the specification of the '606 patent, it is reported that a solution of sodium 2-amino-3-(4-bromobenzoyl)phenylacetate (bromfenac sodium) and BAC in an eye drop is more stable in the presence of a tyloxapol surfactant than in the presence of an ethoxylated carboxylic acid surfactant (polyoxyl 40 stearate) or a polysorbate 80 surfactant. *'606 patent*, Table 1; col. 7, ll. 57-64.

However, tyloxapol is an oligomeric nonionic polyoxyethylated octylphenol surfactant. *Regev*, Scheme 1. The '011 patent teaches that a nonionic polyoxyethylated octylphenol surfactant stabilizes an ophthalmic formulation containing an NSAID and benzalkonium chloride, while formulations using other surfactants did not remain clear and were not stable. *Id.*, col. 12, ll. 26-30. Accordingly, the increased stability of a bromfenac solution containing benzalkonium chloride in the presence of a polyoxyethylated octylphenol surfactant is not an unexpected result; rather, it is expected based on the teachings of the '011 patent. Accordingly, the results relating to stability of bromfenac sodium and BAC in the presence of a tyloxapol surfactant are insufficient to overcome the *prima facie* case of obviousness set forth above.

The '606 patent is listed in the FDA Orange Book with regard to the brand product PROLENSA® (NDA No. 203168). PROLENSA® is the latest in a series of bromfenac containing aqueous ophthalmic solutions. The first marketed solution XIBROM® was a twice daily solution that was discontinued in favor of BROMDAY® which contains polysorbate 80 and 0.09% bromfenac. BROMDAY® does not include any patents listed in the Orange Book, as the '225 patent which describes this formulation has expired. Instead, BROMDAY® was awarded non-patent exclusivity. However, this period of exclusivity expired October 16, 2013.

According to a press release issued on March 27, 2012, the manufacturer of BROMDAY® will discontinue BROMDAY® in favor of PROLENSA®, which has patent coverage through 2025. It is apparent from this strategy that any commercial success associated with current product PROLENSA® is based on the market share built through discontinued products XIBROM® and BROMDAY®, and does not have any nexus to the claims of the '606 patent. Therefore, commercial success, if any, would not overcome the *prima facie* case of obviousness set forth above.

g) Obviousness of Claim 11

The scope of independent claim 11 is substantially similar to independent claim 1, except that claim 11 specifies that greater than about 90% of the original amount of the claimed preparation remains in the preparation after storage at about 60° C for four weeks. Therefore, claim 11 encompasses a method of treating an inflammatory condition of the eye by administering an aqueous liquid preparation comprising bromfenac and tyloxapol in an amount sufficient to stabilize bromfenac. The preparation is ophthalmically administered at a dose and frequency to treat the inflammatory condition. 90% of the preparation remains after storage at about 60° C for four weeks.

As discussed above with regard to claim 1, the '225 patent discloses, in Example 6, an ophthalmic formulation containing the following ingredients:

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	

'225 patent, Example 6.

With regard to Examples 6-8 generally, "[i]t was found that changes in the appearances of the compositions were not observed at all, and the decomposition of the compound was not almost observed [sic], the aqueous compositions being stable, excellent [sic] for a long period of time." *Id., col. 10, ll. 50–57; Table 11.* Specifically with regard to Example 6, the stable aqueous liquid preparation was characterized by 100% of the original amount (*i.e.*, greater than 90%) after 4 weeks at 60° C. *Id., Table 11.* The '011 patent teaches that a nonionic polyoxyethylated octylphenol surfactant stabilizes an ophthalmic formulation containing an NSAID and benzalkonium chloride, while formulations using other surfactants did not remain clear and were not stable. *'011 patent*, col. 12, ll. 26-30. Therefore, the person of ordinary skill in the art would have found enhanced stability to be an inherent property of a formulation containing a nonionic polyoxyethylated octylphenol surfactant, such as Tyloxapol.

In *Santarus v. Par Pharm*, the Federal Circuit found patent claims obvious over the prior art despite the lack of express teaching of a blood plasma concentration obtained from dosing the claimed formulation in the prior art. *Santarus v. Par Pharm*, 694 F.3d 1344, 1354 (Fed. Cir. 2012). The Court stated that the "initial blood serum concentration resulting from administering a PPI dosage is an inherent property of the formulation, and an obvious formulation cannot

become nonobvious simply by administering it to a patient and claiming the resulting serum concentrations." *Id.* The Court asserted that to "hold otherwise would allow any formulation – no matter how obvious – to become patentable merely by testing and claiming an inherent property." *Id.*

As discussed above, the combination of ingredients in the formulation used in the method of claim 1 is obvious over the '225 patent in view of the '804 publication, the '011 patent, and Regev; over the '225 patent in view of the '804 publication, the '011 Patent, Yuan, and the '541 patent; over the '225 patent in view of the '343 patent and the '609 patent; and over the '343 patent in view of the '225 patent and Hara. Claim 11 further limits the formulation used in the claimed method by reciting the inherent property of storage stability under defined conditions that was previously achieved by the prior art. Based on *Santarus*, mere recitation of an inherent stability is insufficient to render an otherwise obvious compound patentable.

Accordingly, the '225 patent in combination with the '804 publication, the '011 patent and Regev explicitly or inherently disclose each and every element of claim 11. Further, the '225 patent in combination with the '804 publication, the '011 patent, Yuan, and the '541 patent disclose each and every element of claim 11. Moreover, the '225 patent in combination with the '343 patent and the '609 patent, or alternatively, the '343 patent in combination with the '225 patent and Hara, disclose each and every element of claim 11. Therefore, claim 11 is *prima facie* obvious.

As also discussed with regard to claim 1, any relevant secondary considerations such as unexpected results or commercial success are insufficient to overcome the case of *prima facie* obviousness. Accordingly, claim 11 is invalid as obvious under 35 U.S.C. § 103(a) over the '225 patent in view of either the '804 publication, the '011 patent, and Regev; or. the '804 publication, the '011 patent, Yuan and the '541 patent; over the '225 patent in view of the 343 patent and the '609 patent, or alternatively, over the '343 patent in view of the '225 patent and Hara.

h) Obviousness of Claim 19

Independent claim 19 is highly similar to claim 1. Claim 19 includes a provision that the preparation does not include mannitol. Claim 1 does not include such a provision. Therefore, consistent with our interpretation of claim 1 we interpret claim 19 to encompass a method of treating an inflammatory condition of the eye by administering an aqueous liquid preparation comprising bromfenac and tyloxapol in an amount sufficient to stabilize bromfenac. The preparation is ophthalmically administered at a dose and frequency to treat the inflammatory condition. The preparation does not include mannitol.

As discussed above, with regard to claims 1 and 11, the '225 patent in combination with the '804 patent, the '011 patent, and Regev discloses the use of an ophthalmic preparation containing bromfenac and tyloxapol to treat inflammatory ophthalmic conditions. The '225 patent in combination with the '804 publication, the '011 patent, Yuan, and the '541 patent also disclose such a method. Further, the '225 patent in combination with the '343 patent and the '609 patent; and the '343 patent in combination with the '225 patent and Hara disclose such a method.

Example 6 of the '225 patent discloses a bromfenac composition that does not include mannitol. Further, none of the formulations of the '225 patent, the '804 publication, or the '343 patent include mannitol. Accordingly, the element of a preparation excluding mannitol for use in a method of treating inflammatory diseases of the eye is disclosed by the prior art.

Therefore, the '225 patent in combination with the '804 publication, the '011 patent and Regev disclose each and every element of claim 19. Further, the '225 patent in combination with the '804 publication, the '011 patent, Yuan, and the '541 patent disclose each and every element of claim 19. Moreover, the '225 patent in combination with the '343 patent and the '690 patent; and the '343 patent in combination with the '225 patent and Hara disclose each and every element of claim 19. Accordingly, claim 19 is *prima facie* obvious.

As also discussed with regard to claims 1 and 11, any relevant secondary considerations such as unexpected results or commercial success are insufficient to overcome the case of *prima facie* obviousness. Accordingly, claim 19 is invalid as obvious under 35 U.S.C. § 103(a) over the '225 patent in view of either the '804 publication, the '011 patent, and Regev; orthe '804 publication, the '011 patent, Yuan and the '541 patent. Further, claim 19 is invalid as obvious under 35 U.S.C. § 103(a) over the '225 patent in view of the '343 patent and the '690 patent, or alternatively, over the '343 patent in view of the '225 patent and Hara.

i) Obviousness of Claims 2, 3, 13, 14, 20, and 21: Particular Diseases

Claims 2, 13, and 20 depend from claims 1, 11, and 19, respectively, and further limit their respective base claims by reciting that the disease is a disease of an anterior or posterior segment of the eye. Claims 3, 14, and 21 depend from claims 2, 13, and 20, respectively, and further limit their respective base claims by reciting that the disease is postoperative inflammation.

Based on the above analysis of claims 1, 11, and 19, claims 2, 3, 13, 14, 20, and 21 are also invalid under 35 U.S.C. § 103(a) as obvious over the '225 patent in view of either the '804 publication, the '011 patent, and Regev; or the '804 publication, the '011 Patent, Yuan, and the '541 patent.

The '011 patent discloses the use of the compositions to treat inflammation caused by eye surgery. *'011 patent*, Abstract. The '804 publication discloses that 3-benzoylphenylacetic acids and derivatives can be used to treat ophthalmic inflammatory conditions including surgically induced inflammation. *'804 publication*, page 2, ll. 8-10. The '343 patent discloses that compositions comprising the NSAID diclofenac potassium can be used for treating any inflammatory condition of the eye, including post operative inflammation. *'343 patent*, Abstract and col. 2, ll. 27-45. Hara describes "[b]romfenac sodium hydrate [as] a type of NSAID that was developed in order to address the needs of clinical sites, and it is indicated for use in a broad range of [ophthalmic] conditions, from inflammation of the outer ocular area to post-operative inflammation of the anterior ocular segment." *Hara*, 1014:1:2. Therefore, the '011 patent, '804

publication, '343 patent, and Hara disclose the additional limitations of claims 2, 3, 13, 14, 20, and 21.

Claims 1, 11, and 19, from which claims 2, 3, 13, 14, 20, and 21 directly or indirectly depend, are invalid as obvious over the '225 patent in view of either the '804 publication, the '011 patent, and Regev; or the '804 publication, the '011 patent, Yuan and the '541 patent. The claims are also invalid as obvious over the '225 patent in view of the '343 patent and the '690 patent, or alternatively, over the '343 patent in view of the '225 patent and Hara. The '011 patent, '804 publication, '343 patent, and Hara disclose the additional limitations of claims 2, 3, 13, 14, 20, and 21. Accordingly, claims 2, 3, 13, 14, 20, and 21 are invalid as obvious under 35 U.S.C. § 103(a) over the '225 patent in view of either the '804 publication, the '011 patent, and Regev; or the '804 publication, the '011 patent, Yuan and the '541 patent. Further, claims 2, 3, 13, 14, 20, and 21 are invalid as obvious under 35 U.S.C. § 103(a) over the '225 patent in view of the '343 patent and the '690 patent, or alternatively, over the '343 patent in view of the '225 patent and Hara.

j) Obviousness of Claims 4 and 22: Bromfenac Sodium Salt

Claims 4 and 22 depend from claims 1 and 19, respectively, and further limit their respective base claims by reciting that the first component in the composition used in the claimed methods is a 2-amino-3-(4-bromobenzoyl)phenylacetic acid (bromfenac) sodium salt.

Example 6 of the '225 patent describes an aqueous liquid preparation containing a sodium salt of bromfenac, specifically the monohydrate of the sodium salt of bromfenac, as required by claims 4 and 22. *'225 patent*, Example 6.

Claims 1 and 19, from which claims 4 and 22 depend, are invalid as obvious over the '225 patent in view of either the '804 publication, the '011 patent, and Regev; or the '804 publication, the '011 patent, Yuan and the '541 patent. The claims are also invalid as obvious over the '225 patent in view of the '343 patent and the '690 patent, or alternatively, over the '343 patent in view of the '225 patent and Hara. The '225 patent discloses the additional limitations of claims 4 and 22. Accordingly, claims 4 and 22 are invalid under 35 U.S.C. § 103(a) as obvious over the '225 patent in view of the '804 publication, the '011 patent, and Regev; or the '804 publication, the '011 Patent, Yuan, and the '541 patent. Further, claims 4 and 22 are invalid as obvious under 35 U.S.C. § 103(a) over the '225 patent in view of the '343 patent and the '690 patent, or alternatively, over the '343 patent in view of the '225 patent and Hara.

k) Obviousness of Claims 5, 6, 8, 15, 16, 23, and 27: Amounts of Bromfenac and Tyloxapol

Claims 5 and 15 depend from claims 1 and 11, respectively, and further limit their respective base claims by reciting that the concentration of tyloxapol in the composition used in the claimed methods is from about 0.01 w/v % to about 0.05 w/v % and the concentration of bromfenac sodium salt is from about 0.01 to about 0.2 w/v %. Claims 6, 16, and 24 depend from claims 5, 15, and 22 respectively, and further limit their respective base claims by reciting that the concentration of the bromfenac sodium salt is from about 0.02 w/v % to about 0.1 w/v %. Claim 8 depends from claim 5 and further limits claim 5 by reciting that the concentration of the

bromfenac sodium salt is about 0.1 w/v %. Claim 23 depends from claim 22 and further limits claims 22 by reciting that the concentration of tyloxapol is from about 0.01 w/v % to about 0.05 w/v % and the concentration of the bromfenac sodium salt is from about 0.05 to about 0.2 w/v %. Claim 27 depends from claim 20 and further limits claim 20 by reciting that the concentration of tyloxapol is from about 0.01 w/v % to about 0.05 w/v %; and that the concentration of bromfenac sodium salt is from about 0.02 to about 0.1 w/v %.

The '225 patent discloses that "[t]o prepare a liquid preparation, the concentration of the active ingredient...is preferably in the range of about 0.01% to about 5%," encompassing the concentration of the bromfenac sodium salt recited in claims 5, 6, 8, 15, 16, 23, 24, and 27. *'225 patent*, col. 4, ll. 42-46. Example 6 of the '225 patent describes an aqueous liquid preparation containing a sodium salt of bromfenac, specifically the monohydrate of the sodium salt of bromfenac, in a concentration of 0.1 g/100 ml (0.1 w/v%), as encompassed by claims 5, 6, 8, 15, 16, 23, 24, and 27. *Id.*, Example 6.

Example 6 of the '225 patent also describes an aqueous liquid preparation containing polysorbate 80 in a concentration of 0.15 g/100 ml (0.15 w/v%). *Id.*

The '804 publication describes topical formulations comprising a 3-benzoylphenylacetic acid or a derivative thereof as the sole active ingredient; polysorbate 80 (0.01 w/v%); and benzalkonium chloride. *'804 publication*, Formulations 1 and 2 on pages 6-7. The '804 publication also describes a topical formulation comprising a derivative of 3-benzoylphenylacetic acid, nepafenac, as the sole active ingredient; tyloxapol (0.01 w/v%); and benzalkonium chloride. *Id.*, Formulation 3 on page 7.

Regev teaches that the oligomeric surfactant tyloxapol has a critical micelle concentration of 0.0016 mM. *Regev*, page 11. Polysorbate 80 is known to have a critical micelle concentration of 0.012 mM.[11] Tyloxapol is thus a surfactant with a lower critical micelle concentration than that of polysorbate 80.

Tyloxapol and polysorbate 80 are used in the same concentration by Formulations 1 and 3 of the '804 publication, specifically 0.01 w/v%. *'804 publication*, Formulations 1 and 3. Accordingly, the '804 publication teaches that tyloxapol may be substituted for polysorbate 80 at a concentration of 0.01 w/v%. Further motivation to use tyloxapol at a concentration of 0.01 w/v%, rather than a surfactant concentration of 0.15 w/v% as described by the '804 publication, is found in the teachings of Regev that tyloxapol has a lower critical micelle concentration than that of polysorbate 80. Accordingly, a person of ordinary skill in the art would understand that Tyloxapol may be used in a smaller amount than polysorbate 80. Therefore, it would have been *prima facie* obvious to a person of ordinary skill in the art to modify the formulation of Example 6 of the '225 patent by replacing polysorbate 80 in a concentration of 0.15 w/v%, as used by the '225 patent, with 0.01 w/v% of tyloxapol, as encompassed by claims 5, 15, 23, and 27. Accordingly, the '225 patent and the '804 patent disclose the additional limitations of claims 5, 6, 8, 15, 16, 23, 24, and 27.

[11] See http://www.gbiosciences.com/ResearchProducts/PGDTween80-desc.aspx.

In the alternative, the '343 patent describes an ophthalmic formulation containing diclofenac (an acidic NSAID), BAC, and tyloxapol with express disclosure of tyloxapol concentrations of 1.0 mg/ml and 0.1 mg/ml, *i.e.*, 1 and 0.1 w/v%, in Examples 2 and 3 respectively.

Further, absent criticality, "[i]t is not inventive to discover the optimum or workable ranges by routine experimentation." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1368 (Fed. Cir. 2007), *quoting In re Geisler*, 116 F.3d 1465, 1470 (Fed. Cir. 1997).

Claims 1, 11, and 19, from which claims 5, 6, 8, 15, 16, 23, 24, and 27 directly or indirectly depend, are invalid as obvious over the '225 patent in view of either the '804 publication, the '011 patent, and Regev; or the '804 publication, the '011 patent, Yuan and the '541 patent. The claims are also invalid as obvious over the '225 patent in view of the '343 patent and the '690 patent, or alternatively, over the '343 patent in view of the '225 patent and Hara. The '225 patent and the '804 publication disclose the additional limitations of claims 5, 6, 8, 15, 16, 23, and 27. Accordingly, claims 5, 6, 8, 15, 16, 23, 24, and 27 are each invalid as obvious under 35 U.S.C. § 103(a) over the '225 patent in view of either the '804 publication, the '011 patent, and Regev; or the '804 publication, the '011 patent, Yuan and the '541 patent. Further, claims 5, 6, 8, 15, 16, 23, and 27 are invalid as obvious under 35 U.S.C. § 103(a) over the '225 patent in view of the '343 patent and the '690 patent, or alternatively, over the '343 patent in view of the '225 patent and Hara.

l) Obviousness of Claims 7 and 17: Quaternary Ammonium Salt

Claims 7 and 17 depend from claims 5 and 11, respectively, and further limit their respective base claims by reciting that the preparation used in the claimed methods includes a quaternary ammonium salt.

Benzalkonium chloride is defined in the specification of the '606 patent as a quaternary ammounium salt. *'606 patent*, col. 2, ll. 19-25.

Example 6 of the '225 patent describes an aqueous liquid preparation containing a sodium salt of bromfenac, specifically the monohydrate of the sodium salt of bromfenac, and benzalkonium chloride, a quaternary ammonium salt. *'225 patent*, Example 6. The '804 publication also describes a topical formulation comprising a derivative of 3-benzoylphenylacetic acid, nepafenac, as the sole active ingredient; tyloxapol; and benzalkonium chloride. *'804 publication*, Formulation 3 on page 7. Therefore, each of the '225 patent and the '804 publication disclose the additional limitation of claims 7 and 17.

Further, the '011 patent teaches the use of specific surfactants to further stabilize NSAID and BAC formulations. In addition, the '343 patent's Example 2 includes BAC in its described NSAID formulation.

As discussed above, claims 5 and 11, from which claims 7 and 17 depend, are invalid as obvious over the '225 patent in view of either the '804 publication, the '011 patent, and Regev; or the '804 publication, the '011 patent, Yuan and the '541 patent. The claims are also invalid as obvious over the '225 patent in view of the '343 patent and the '690 patent, or alternatively, over

the '343 patent in view of the '225 patent and Hara. The '225 patent, the '804 publication, the '011 patent, and the '343 patent each disclose the additional limitation of claims 7 and 17. Therefore, claims 7 and 17 are each invalid as obvious under 35 U.S.C. § 103(a) over the '225 patent in view of either the '804 publication, the '011 patent, and Regev; or the '804 publication, the '011 patent, Yuan and the '541 patent. Further, claims 7 and 17 are invalid as obvious under 35 U.S.C. § 103(a) over the '225 patent in view of the '343 patent and the '690 patent, or alternatively, over the '343 patent in view of the '225 patent and Hara.

m) Obviousness of Clams 9, 18 and 25: Specific Formualtions

Claim 9 depends from claim 1 and further limits claim 1 by reciting that the formulation used in the claimed method consists essentially of:

bromfenac sodium salt at a concentration of from about 0.02 w/v % to about 0.1 w/v %;

sodium tetraborate;

EDTA sodium salt;

benzalkonium chloride;

polyvinyl pyrrolidone; and

sodium sulfite.

Claims 18 and 25 depend from claims 11 and 20, respectively. Claims 18 and 26 further limit their respective base claims by reciting that the formulation used in the claimed methods consists essentially of:

bromfenac sodium salt at a concentration of from about 0.02 w/v % to about 0.1 w/v %;

tyloxapol;

boric acid;

sodium tetraborate;

EDTA sodium salt;

benzalkonium chloride;

polyvinyl pyrrolidone; and

sodium sulfite.

Claims 9, 18, and 25 contain the transitional phrase "consists essentially of." The transitional phrase "consisting essentially of" is partially closed in that the phrase allows only additional materials or steps "that do not materially affect the basic and novel characteristics" of the claimed invention. *In re Herz*, 537 F.2d 549, 551-52, (C.C.P.A. 1976).

During prosecution of the parent '006 application, the language "consisting essentially of" was defined so as to exclude prior art formulations including a second active ingredient, in addition to an NSAID.

> [T]he claim recites the transitional phrase "consisting essentially of" means that the claim is limited to the specified ingredients and those that do not materially affect the basic and novel characteristics of the claimed invention. See M.P.E.P. 2111.03.
>
> It is respectfully submitted that the principal 5-HT agonist of the Gamache composition would affect the basic novel properties of the claimed preparation.

Prosecution History of the '006 application, Response dated March 26, 2008.

The specification describes bromfenac compositions that include a preservative and tyloxapol and are stable. Accordingly, claims 9, 18, and 25 are properly interpreted to require an aqueous liquid preparation consisting essentially of bromfenac sodium salt at a concentration of from about 0.02 w/v % to about 0.1 w/v %; tyloxapol; boric acid; sodium tetraborate (borax); EDTA sodium salt (edetate sodium salt); benzalkonium chloride; polyvinylpyrrolidone; and sodium sulfite. The preparations do not exclude other components provided that the preparation is stable.

Example 6 of the '225 patent discloses a preparation containing bromfenac sodium salt at a concentration of 0.1 w/v%, polysorbate 80, boric acid, borax (i.e., sodium tetraborate), disodium edetate (i.e., EDTA sodium salt), benzalkonium chloride, polyvinylpyrrolidone, and sodium sulfite. *'225 patent*, Example 6.

As discussed above, the '804 publication describes a topical formulation comprising a derivative of 3-benzoylphenylacetic acid, as the sole active ingredient; polysorbate 80; and benzalkonium chloride. *'804 publication*, Formulation 1 on page 6. The '804 publication also describes a topical formulation comprising a derivative of 3-benzoylphenylacetic acid, nepafenac, as the sole active ingredient; tyloxapol; and benzalkonium chloride. *'804 publication*, Formulation 3 on page 7.

As discussed above, it would have been obvious to substitute the polysorbate 80 of the '225 patent with the tyloxapol of the '804 patent in view of the teachings of the '011 patent and Regev and in view of the teachings of the '011 patent, Yuan, and the '541 patent. The substituted preparation would have inherently been stable. Therefore, the combination of the '225 patent and the '804 patent disclose the additional limitations of claims 9, 18, and 25.

Further, a person of ordinary skill in the art would have had motivation to substitute, and a reasonable expectation of success in substituting, tyloxapol from Example 2 of the '343 patent for polysorbate 80, because the '225 patent provides working examples of bromfenac preparations formulated with polysorbate 80 and the '609 patent teaches that tyloxapol is superior to polysorbate 80 in solubilizing acidic ophthalmic drugs.

As discussed above, claims 1, 11, and 20, from which claims 9, 18, and 25 depend, are invalid under 35 U.S.C. § 103(a) as obvious over the '225 patent in view of either the '804 publication, the '011 patent, and Regev; or the '804 publication, the '011 patent, Yuan, and the '541 patent. The claims are also invalid as obvious over the '225 patent in view of the '343 patent and the '690 patent, or alternatively, over the '343 patent in view of the '225 patent and Hara. The combination of the '225 patent and the '804 publication or the combination of the '225 and the '343 patents disclose the additional limitations of claims 9, 18, and 25. Therefore, claims 9, 18, and 25 are each invalid as obvious under 35 U.S.C. § 103(a) over the '225 patent in view of either the '804 publication, the '011 patent, and Regev; or the '804 publication, the '011 patent, Yuan, and the '541 patent. Further, claims 7 and 17 are invalid as obvious under 35 U.S.C. § 103(a) over the '225 patent in view of the '343 patent and the '690 patent, or alternatively, over the '343 patent in view of the '225 patent and Hara.

n) Obviousness of Claim 10: Dose

Claim 10 depends from claim 1 and further limits claim 1 by reciting that the dose comprises one or two drops.

The '225 patent discloses administering bromfenac compositions at a dose of one to several drops. *'225 patent*, col. 4, ll. 50-55. The '804 publication discloses administering ophthalmic preparations at a dose of 1-2 drops. *'804 publication*, page 6, ll. 1-10. Hara discloses that ophthalmic solutions comprising bromfenac sodium hydrate and benzalkonium chloride are used twice a day, with the installation of 1-2 drops per dose. *Hara*, 1015:1:2. Therefore, each of the '225 publication, the '804 publication, and Hara disclose the additional limitation of claim 10.

Claim 1, from which claim 10 depends, is invalid as obvious over the '225 patent in view of either the '804 publication, the '011 patent, and Regev; or the '804 publication, the '011 patent, Yuan and the '541 patent. The claims are also invalid as obvious over the '225 patent in view of the '343 patent and the '690 patent, or alternatively, over the '343 patent in view of the '225 patent and Hara. The'225 patent, the '804 publication, and Hara disclose the additional limitation of claim 10. Therefore, claim 10 is invalid as obvious under 35 U.S.C. § 103(a) over the '225 patent in view of either the '804 publication, the '011 patent, and Regev; or the '804 publication, the '011 patent, Yuan and the '541 patent. Further, claim 10 is invalid as obvious under 35 U.S.C. § 103(a) over the '225 patent in view of the '343 patent and the '690 patent, or alternatively, over the '343 patent in view of the '225 patent and Hara.

o) Obviousness of Claims 12 and 26: Storage Stability

Claim 12 depends from claim 11, and further limits claim 11 by reciting that the stable aqueous liquid preparation used in the claimed method is characterized in that greater than about 92% of the original amount of bromfenac remains in the preparation after storage at about 60° C for 4 weeks. Claim 26 depends from claim 20 and further limits claim 20 by reciting that the stable aqueous liquid preparation used in the claimed method is characterized in that greater than about 90% of the original amount of bromfenac remains in the preparation after storage at about 60° C for 4 weeks. Thus, claims12 and 26 each further limit their respective base claims only by reciting a property of storage stability.

Claims 11 and 20, from which claims 12 and 26 depend, are invalid under 35 U.S.C. § 103(a) as obvious over the '225 patent in view of the '804 publication, the '011 patent, and Regev; and as obvious over the '225 patent in view of the '804 publication, the '011 Patent, Yuan, and the '541 patent. The claims are also invalid as obvious over the '225 patent in view of the '343 patent and the '690 patent, or alternatively, over the '343 patent in view of the '225 patent and Hara.

The '225 patent teaches a stable aqueous liquid preparation having greater than about 90% of the original amount of bromfenac after 4 weeks at 60° C. *'225 patent*, Table 11. The '011 patent teaches that a nonionic polyoxyethylated octylphenol surfactant stabilizes an ophthalmic formulation containing an NSAID and benzalkonium chloride, while formulations using other surfactants did not remain clear and were not stable. *'011 patent*, col. 12, ll. 26-30. Therefore, the person of ordinary skill would have found enhanced stability to be an inherent property of a formulation containing a nonionic polyoxyethylated octylphenol surfactant, such as Tyloxapol. The precise extent of the enhanced stability is an inherent property of the specific formulation.

In *Santarus v. Par Pharm*, the Federal Circuit found patent claims obvious over the prior art despite the lack of express teaching of a blood plasma concentration obtained from dosing the claimed formulation in the prior art. *Santarus v. Par Pharm*, 694 F.3d 1344, 1354 (Fed. Cir. 2012). The Court stated that the "initial blood serum concentration resulting from administering a PPI dosage is an inherent property of the formulation, and an obvious formulation cannot become nonobvious simply by administering it to a patient and claiming the resulting serum concentrations." *Id.* The Court asserted that to "hold otherwise would allow any formulation—no matter how obvious—to become patentable merely by testing and claiming an inherent property." *Id.*

Accordingly, claims 12 and 26 are invalid under 35 U.S.C. § 103(a) as obvious over the '225 patent in view of the '804 publication, the '011 patent, and Regev; and as obvious over the '225 patent in view of the '804 publication, the '011 Patent, Yuan, and the '541 patent. Further, claims 12 and 26 are invalid as obvious under 35 U.S.C. § 103(a) over the '225 patent in view of the '343 patent and the '690 patent, or alternatively, over the '343 patent in view of the '225 patent and Hara.

p) Obviousness of Claims 28, 29 and 30: Preservative Efficacy Standard

Claims 28, 29, and 30 depend from claims 1, 11, and 19, respectively, and further limit their base claims by reciting that the aqueous liquid preparation used in the claimed methods further satisfies the preservative efficacy standard of EP-criteria B of the European Pharmacopoeia as follows:

> viable cell counts of bacteria (*S. aureus*, *P. aeruginosa*) 24 hours and 7 days after inoculation decrease to not more than 1/10 and not more than 1/1000, respectively, and thereafter, the cell count levels off or decreases; and

> viable cell count of fungi (*C. albicans*, *A. niger*) 14 days after inoculation decreases to not more than 1/10, and thereafter, the cell count keeps the same level as that of 14 days after inoculation.

Thus, claims 28, 29, and 30 each further limit their respective base claims only by reciting properties of preservative efficacy in the presence of microbes, based on known standards.

Claims 1, 11, and 19, from which claims 28, 29, and 30 depend, are invalid under 35 U.S.C. § 103(a) as obvious over the '225 patent in view of either the '804 publication, the '011 patent, and Regev; or the '804 publication, the '011 patent, Yuan, and the '541 patent. The claims are also invalid as obvious over the '225 patent in view of the '343 patent and the '690 patent, or alternatively, over the '343 patent in view of the '225 patent and Hara.

The '011 patent teaches that a nonionic polyoxyethylated octylphenol surfactant stabilizes an ophthalmic formulation containing an NSAID and benzalkonium chloride, while formulations using other surfactants did not remain clear and were not stable. *'011 patent*, col. 12, ll. 26-30. The '011 patent is directed to a preservative system including a quaternary ammonium preservative and a stabilizing amount of a nonionic surfactant. *Id.*, col. 7, ll. 13-15. "Preservative efficacy of the formulation prior to administration is tested by the procedure described in the U.S. Pharmacopeia Compendiary, whereby a solution is challenged with a panel of microbes and a determination is made as to whether a given microbe survives in it." *Id.*, col. 8, ll. 58-63. Thus, the '011 patent describes formulations having defined properties of preservative efficacy in the presence of microbes, based on known standards.

For the reasons discussed herein, the person of ordinary skill in the art would have found preservative efficacy to be an inherent property of a formulation containing a nonionic polyoxyethylated octylphenol surfactant, as taught by the '011 patent. The precise extent of the enhanced stability is necessarily an inherent property of the specific formulation.

In *Santarus v. Par Pharm*, the Federal Circuit found patent claims obvious over the prior art despite the lack of express teaching of a blood plasma concentration obtained from dosing the claimed formulation in the prior art. 694 F.3d 1344, 1354 (Fed. Cir. 2012). The Court stated that the "initial blood serum concentration resulting from administering a PPI dosage is an inherent property of the formulation, and an obvious formulation cannot become nonobvious simply by administering it to a patient and claiming the resulting serum concentrations." *Id.* The Court asserted that to "hold otherwise would allow any formulation—no matter how obvious—to become patentable merely by testing and claiming an inherent property." *Id.*

Accordingly, claims 28, 29, and 30 are invalid under 35 U.S.C. § 103(a) as obvious over the '225 patent in view of either the '804 publication, the '011 patent, and Regev; or the '804 publication, the '011 patent, Yuan, and the '541 patent. Further, claims 12 and 26 are invalid as obvious under 35 U.S.C. § 103(a) over the '225 patent in view of the '343 patent and the '690 patent, or alternatively, over the '343 patent in view of the '225 patent and Hara.

D. NON-INFRINGEMENT OF THE '606 PATENT

As set forth in detail above, each of claims of the '606 patent is invalid under 35 U.S.C. § 103. Because the claims of the '606 patent are invalid, Innopharma cannot infringe any of these claims.

EXHIBIT B

From: Awuah, Kwadwo [mailto:Kwadwo.Awuah@fda.hhs.gov]
Sent: Wednesday, September 17, 2014 2:12 PM
To: Christy Meng
Cc: Margand, Iain; Young, Johnny
Subject: RE: ANDA206326 Bromfenac Oph. Solution 0.07% -Notice by FedEx
Importance: High

Dear Ms. Meng,

It is permissible to utilize UPS/FedEx/DHL in lieu of USPS when sending notification to the patent holder(s) and/or assignee(s) that ANDA 206326 has been accepted for filing by the Office of Generic Drugs (OGD) with a Paragraph IV certification.

Please include a copy of this email when submitting an amendment to OGD containing proof of delivery of notice letters.

Best regards,

Kojo
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