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October 30, 2014

CONFIDENTIAL

VIA FEDEX OVERNIGHT DELIVERY[1]

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President & CEO
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1 Bausch & Lomb Place
Rochester, NY 14604

Re: ANDA No. 206326 (Bromfenac) Notification of Certification of Noninfringement and/or Invalidity for U.S. Patent No. 8,754,131 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 21 C.F.R. § 319.94(a)(12)(i)(A)(4) ("Paragraph IV"), that U.S. Patent No. 8,754,131 ("the '131 patent")

[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 '131 patent is taken from the face page of the '131 patent. The USPTO's web-based assignment records accessed on October 30, 2104 report that the assignment data for the '131 patent is not currently available.

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. Innopharma has amended its ANDA under 21 C.F.R. § 314.94(a)(12)(vi) to further include a Paragraph IV certification to the '131 patent, which lists as an issuance date on its face of July 17, 2014. Each of the '131, '431 and '290 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. With regard to the '131 patent, according to the FDA's Orange Book:

- the '131 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 '131 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
Tel: (212) 210-9400
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

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.

EXHIBIT A

Table of Contents

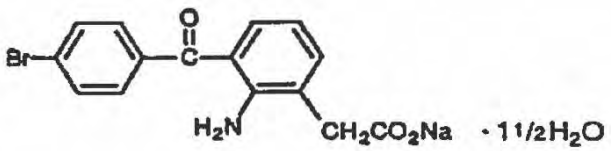
EXHIBIT A
DETAILED STATEMENT OF THE FACTUAL AND LEGAL BASIS FOR INNOPHARMA LICENSING INC.'S CERTIFICATION THAT U.S. PATENT NO. 8,754,131 IS INVALID, UNENFORCEABLE, AND/OR WILL NOT BE INFRINGED BY THE MANUFACTURE, USE, SALE, OFFER FOR SALE, OR IMPORTATION OF INNOPHARMA'S BROMFENAC PRODUCT AS DEFINED BY ANDA NO. 206-326

For at least the reasons set forth below, U.S. Patent No. 8,754,131 ("the '131 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 '131 patent; U.S. Patent No. 8,128,431 ("the '431 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 the Notification letter dated September 19, 2014 and related exhibits, the combined contents of which provided notice to the NDA holder and assignee of the '431 and '290 patents and set forth the factual and legal bases for Innopharma's certification that 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 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 '131 patent for at least the following reasons:[2]

The '131 Patent

As set forth in detail below, Innopharma cannot infringe claims 1-30 of the '431 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 8,754,131 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 1-3, 5, 7-9, 11, 13-15, 17, and 19-22 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).

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).

[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.

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,

[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).

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. 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

[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).

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).

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").

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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).

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. 8,754,131

1. Priority Information and Related Applications

U.S. Patent Number 8,754,131 ("the '131 patent") ("Exhibit 2") issued on June 17, 2014, from Application Serial Number 14/165,976 ("the '976 application"), filed as 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 '131 Patent

The thirty claims of the '131 patent are listed below:

> 1. A stable aqueous liquid preparation comprising: (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 and is present in the preparation at a concentration from about 0.05 w/v % to about 0.2 w/v %; the second component is tyloxapol and is present in said liquid preparation in an amount sufficient to stabilize said first component; and wherein said stable liquid preparation is formulated for ophthalmic administration.

2. The aqueous liquid preparation according to claim 1, further comprising a quaternary ammonium salt.

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

4. The aqueous liquid preparation according to claim 1, wherein the concentration of tyloxapol is from about 0.01 w/v % to about 0.05 w/v %.

5. The aqueous liquid preparation according to claim 1, wherein the pH is from about 7.5 to about 8.5.

6. The stable aqueous liquid preparation of claim 1; wherein the stable aqueous liquid preparation consists essentially of: (a) 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt, (b) tyloxapol, (c) boric acid, (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, 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 %, and wherein the concentration of tyloxapol is from about 0.01 w/v % to about 0.05 w/v %.

7. A stable aqueous liquid preparation comprising: (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 and is present in the preparation at a concentration from about 0.05 w/v % to about 0.2 w/v %; the second component is tyloxapol; wherein said stable liquid preparation is formulated for ophthalmic administration; and wherein the stable aqueous liquid preparation is characterized in that greater than about 90% of the original amount of the first component remains in the preparation after storage at about 60° C. for 4 weeks.

8. The aqueous liquid preparation according to claim 7, further compris-ing a quaternary ammonium salt.

9. The stable aqueous liquid preparation of claim 7; 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.

10. The aqueous liquid preparation according to claim 7; 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 0.05 w/v % to about 0.1 w/v %.

11. The aqueous liquid preparation according to claim 10, wherein the pH is from about 7.5 to about 8.5.

12. The stable aqueous liquid preparation of claim 7; 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 0.05 w/v % to about 0.1 w/v %, and the con-centration of tyloxapol is about 0.02 w/v %.

13. A stable aqueous liquid preparation comprising: (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 and is present in the preparation at a concentration from about 0.05 w/v % to about 0.2 w/v %; the second component is tyloxapol; wherein said stable liquid preparation is formulated for ophthalmic administration; provided that the liquid preparation does not include mannitol.

14. The aqueous liquid preparation according to claim 13, further comprising a quaternary ammonium salt.

15. The aqueous liquid preparation according to claim 13, wherein the first component is a 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt.

16. The aqueous liquid preparation according to claim 13, 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 0.1 w/v %.

17. The aqueous liquid preparation according to claim 13, wherein the pH is from about 7.5 to about 8.5.

18. The stable aqueous liquid preparation of claim 13; 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 %, and the con-centration of tyloxapol is from about 0.02 w/v % to about 0.05 w/v %.

19. The stable aqueous liquid preparation of claim 13; 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.

20. The stable aqueous liquid preparation according to claim 19, further comprising a quaternary ammonium salt.

21. The stable aqueous liquid preparation of claim 19; 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.

22. The stable aqueous liquid preparation according to claim 21, 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 0.05 w/v % to about 0.1 w/v %.

23. The aqueous liquid preparation according to claim 22, wherein the pH is from about 7.5 to about 8.5.

24. The stable aqueous liquid preparation of claim 13; 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 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 0.05 w/v % to about 0.1 w/v %.

25. The aqueous liquid preparation of claim 1, wherein the aqueous liquid preparation further satisfies the preservative efficacy standard of US 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.

26. The aqueous liquid preparation of claim 4, wherein the aqueous liquid preparation further satisfies the preservative efficacy standard of US 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.

27. The aqueous liquid preparation of claim 7, wherein the aqueous liquid preparation further satisfies the preservative efficacy standard of US 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.

28. The aqueous liquid preparation of claim 9, wherein the aqueous liquid preparation further satisfies the preservative efficacy standard of US 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 aqueous liquid preparation of claim 13, wherein the aqueous liquid preparation further satisfies the preservative efficacy standard of US 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 aqueous liquid preparation according to claim 1, further com-prising one or more additives selected from the group consisting of a preservative, buffer, thickener, stabilizer, chelating agent, and pH con-trolling agent..

3. Specification of the '131 Patent

The specification of the '131 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." *'131 patent, col. 1, ll. 8-17.* 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. 11-18.*

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. 8-62.* 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 '131 Patent

The prosecution history of the '131 patent is attached as Exhibit 3. The '131 patent was filed as Application Serial Number 14/165,976 ("the '976 application"). The '976 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 January 28, 2014, in favor of new claims 19-48. *Prosecution History of the '131 patent*; Preliminary Amendment dated January 28, 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) Office Action dated March 13, 2014

In an Office Action dated March 13, 2014, the Examiner rejected claims 19-48 on the ground of nonstatutory double patenting as being unpatentable over:

claims 1-22 of U.S. Patent No. 8,129,431;

claims 1-17 of U.S. Patent No. 8,497,304; and

claims 1-30 of U.S. Patent No. 8,669,290.

Id., Office Action dated March 13, 2014.

iii) Response dated March 20, 2014

A response dated March 20, 2014, was filed. *Id.*, Response dated March 20, 2014. In their response, the Applicants addressed the rejections on the ground of nonstatutory double patenting over claims of US. Patent Nos. 8,129,431; 8,497,304; and 8,669,290 by submitting a Terminal Disclaimer over each these patents. *Id.*

iv) Notice of Allowance

A Notice of Allowance was issued on April 21, 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 '131 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:

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

> 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 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.*

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[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.

In their response, the Applicants noted that the Examiner had agreed that each of the above grounds of rejection would be withdrawn. *Id.*

The Applicants next addressed the rejection over Gamache and ISTA Pharmaceuticals or Nolan. *Id.* The Applicants alleged that Gamache was directed to compositions comprising 5-HT1D and/or HT1B agonists, and did not disclose the specific claimed combination. *Id.* The Applicants further alleged that neither ISTA Pharmaceuticals nor Nolan disclosed an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester. *Id.*

> [I]t is respectfully submitted that neither Gamache et al., ISTA Pharmaceuticals and/or Nolan disclose or suggest the claimed preparation as amended, because they do not disclose the claimed preparation comprises the at least first and second claimed components.

Id.

With regard to claim 41, the Applicants argued that the claim was allowable over Gamache and ISTA Pharmaceuticals or Nolan, as claim 41 included the transitional phrase "consisting essentially of," which excludes ingredients which "materially affect the basic and novel characteristics of the claimed invention." *Id.* According to the Applicant, "the principal 5-HT agonist of the Gamache composition would affect the basic novel properties of the claimed preparation." *Id.*

The Applicant addressed the rejection under 35 U.S.C. § 103 over Yakuji Nippo and Xia by alleging that Xia added tyloxapol to a contact lens solution for "improving stability of the biguanide disinfection agent in the solution." *Id.* "Yakuji contains bromfenac and does not contain any biguanide..." *Id.* "Therefore it is respectfully submitted that one skilled in the art would not have been motivated to add tyloxapol taught by Xia to the composition of Yakuji for the purpose of stabilizing bromfenac." *Id.* The Applicant addressed the rejection under 35 U.S.C. § 103 over Yakuji Nippo and Xia and Nolan by alleging that Nolan "fails to remedy the deficiencies of Yakuji and Xia." *Id.*

iv) Office Action dated July 18, 2008

In the Office Action dated July 18, 2008, the Examiner withdrew all rejections under 35 U.S.C. § 102. *Id.*, Office Action dated July 18, 2008. The rejections over Yakuji Nippo Ltd. and Xia, alone or in combination with Nolan, were also withdrawn. *Id.*

Claims 41 and 63 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite due to the language "consisting essentially of at least," which could be construed as being either open or closed. *Id.*

The Examiner also maintained the rejection of claim 19 under 35 U.S.C. § 103(a) as being unpatentable over Gamache and ISTA Pharmaceuticals or Nolan, and further applied this rejection to claims 41 and 63. *Id.*

> Applicant argues that Gamache does not suggest the claimed invention, because Gamache is directed to 5-HT agonists compositions with a great number of other

> possible ingredients; the reference does not suggest the required combination of bromfenac and tyloxapol. This is not persuasive. Gamache clearly teaches combinations of 5-HT1B/1D agonists with one or more anti-inflammatory agents, dosed concurrently or sequentially...This implies...two different compositions, where the first contains only an antiinflammatory agent as the active compound, the second contains only a 1B/1D agonist as active agent (implied by sequential dosing).

Id.

Claims 19, 41, and 63 were rejected under 35 U.S.C. 103(a) as being unpatentable over Hellberg et al. (US 5,998,465) and Nolan. *Id.* Hellberg was relied upon to show topical ophthalmic formulations of anti-inflammatory compounds, including bromfenac esters, which include tyloxapol at 0.01-0.05 w/v %, HPMC (thickener), benzalkonium chloride (preservative), and edetate disodium (chelating agent) at a pH of 7.4. *Id.* "It would have been obvious for one of ordinary skill in the art at the time of the invention to substitute bromfenac, taught by Nolan for the compounds of Hellberg." *Id.*

v) Response dated January 15, 2009

A response, dated January 15, 2009, was filed after an Examiner's Interview held on November 20, 2008.[8] *Id.*, Response dated March 26, 2008. In that response, the Applicants amended claims 19, 41, and 63 to recite that the claimed aqueous liquid preparations are "in the form of an eye drop." *Id.* The Applicant alleged that:

> One skilled in the art would not have been motivated to modify the Gamache et al. composition in view of ISTA and Nolan, to arrive at the claimed eye drop. The primary object of Gamache et al. is to make a composition containing an IB/ID agonist. The artisan would not have been motivated by the reference to make a composition lacking the IB/ID agonist.

Id.

The Applicant also alleged that the bromfenac esters of Hellberg contain both anti-inflammatory and antioxidant moieties. *Id.* Further, Hellberg et al. purportedly "explicitly state that the principle of operation of the anti-inflammatory and [antioxidant] compounds is to provide...compounds with not only anti-inflammatory activity, but also anti-oxidant activity for improved therapeutic functionality:" *Id.* The Applicant alleged that substitution of the compounds of Hellberg et al. with bromfenac, which is not an anti-oxidant, would render the Hellberg et al. invention "unsatisfactory for its intended purpose of providing 'compounds having potent antiinflammatory and anti-oxidant activity.'" *Id.*

[8] While an Interview Summary Form is present in the file history, the Applicant's summary of the Interview is relied upon herein.

vi) Office Action dated June 3, 2009

In a final Office Action dated June 3, 2009, claims 19, 41, and 63 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. *Id.*, Office Action dated June 3, 2009. "It is unclear what is meant by 'in the form of an eye drop.' ...It is suggested that the claim be amended to recite 'wherein said liquid preparation is formulated for ophthalmic administration.'" *Id.* The Examiner maintained the rejection under 35 U.S.C. § 103(a) over Gamache and ISTA Pharmaceuticals or Nolan; and the rejection under 35 U.S.C. § 103(a) over Hellberg et al. (US 5,998,465) and Nolan. *Id.*

vii) RCE and Rejection

In an RCE dated October 5, 2009, the Applicant accepted the Examiner's suggestion regarding the rejection under 35 U.S.C. § 112, second paragraph, by amending all independent claims to recite a liquid preparation "formulated for ophthalmic administration." *Id.*, RCE dated Oct. 5, 2009.

In an Office Action dated December 24, 2009, the Examiner continued to maintain all pending rejections under 35 U.S.C. § 103(a).

viii) Response dated March 24, 2010

In a response dated March 24, 2010, the Applicant addressed the rejection under 35 U.S.C. § 103(a) by canceling claims 19 and 63. *Id.*, Response dated March 24, 2010. The Applicant amended claim 41 as follows:

> 41. (Currently amended) An aqueous liquid preparation consisting essentially of ~~at least~~ the following two components, wherein the first component ~~comprising~~ is 2-amino-3-(4bromobenzoyl) phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and the second component ~~comprising~~ is an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester, wherein said liquid preparation is formulated for ophthalmic administration.

Id. The Applicant also added new claim 64, as follows:

> 64. (New) An aqueous liquid preparation consisting 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,

(h) sodium sulfite, and wherein said liquid preparation is formulated for ophthalmic administration.

Regarding the rejection under 35 U.S.C. 103(a) over Hellberg et al. (US 5,998,465) and Nolan, the Applicants again alleged that substitution of the compounds of Hellberg et al. with bromfenac would render the Hellberg et al. invention unsatisfactory for its intended purpose. *Id.*

ix) Office Action dated June 24, 2010

In a final Office Action dated June 24, 2010, the rejection of claim 41 under 35 U.S.C. 103(a) as being unpatentable over Hellberg et al. (US 5,998,465) and Nolan was withdrawn. *Id.*, Office Action dated June 3, 2009. The Examiner entered a new ground of rejection. *Id.*

Claim 41 was rejected under 35 U.S.C. § 102(b) as being anticipated by Desai (U.S. 5,603,929).

> Desai et al. teach an ophthalmic composition comprising bromfenac (2-amino-3-(4-bromobenzoyl)phenylacetic acid) and its ophthalmically acceptable salts, esters, amides or prodrugs thereof...and polysorbates such as tweens and tyloxapol and further comprising boric acid buffer...

Id.

x) Response dated October 25, 2010

In a Response dated October 25, 2010, claims 41 and 64 were amended as follows:

> 41. (Currently amended) An aqueous liquid preparation consisting essentially of the following two components, wherein the first component is 2-amino-3-(4bromobenzoyl) phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and the second component is an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester, wherein said liquid preparation is formulated for ophthalmic administration, and wherein when a quaternary ammonium compound is included in said liquid preparation, the quaternary ammonium compound is limited to benzalkonium chloride.
>
> 64. (Currently amended) An aqueous liquid preparation consisting 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,

(h) sodium sulfite, ~~and~~

wherein said liquid preparation is formulated for ophthalmic administration, and

wherein benzalkonium chloride is the only quaternary ammonium compound which is included in said liquid preparation.

Id.

The Applicants alleged that Desai taught that benzalkonium chloride and other quaternary ammonium compounds are generally considered to be incompatible with ophthalmic compositions of drugs with acidic groups, such as bromfenac. *Id.* It was alleged that Desai instead required use of a polymeric quaternary ammonium compound, excluded from the claimed composition. *Id.*

xi) Office Action of May 6, 2011 and Interview of September 1, 2011

In an Office Action dated May 6, 2011, the Examiner rejected claim 41 under 35 U.S.C. § 103(a) over Yanni (5475034) in view of Guy (5540930). *Id.*, Office Action dated May 6, 2011. "Yanni et al. teaches a composition comprising an active agent…(3-benzoylphenylacetic acid derivatives, salts are known) in 0.01-0.5%, polysorbate 80 in 0.01 %, benzalkonium chloride, disodium EDTA, monobasic sodium phosphate, dibasic sodium phosphate, sodium chloride, pH adjustment with NaOH and/or HCI, water." *Id.* The Examiner relied upon Guy to teach tyloxapol. *Id.* "It would have been obvious to one of ordinary skill in the art…to interchange polysorbate 80 and tyloxapol. The motivation comes from the teaching of Guy et al. that both compounds are non-ionic surfactant surface active agents." *Id.*

In an Examiner's Interview dated September 1, 2011, the Applicant agreed to consider limiting the claims to Bromfenac and tyloxapol, and to delete the method claims. *Id.*, Interview Summary Form dated September 1, 2011.

xii) Response dated September 6, 2011

In a Response dated September 6, 2011, the Applicant amended claim 41 as follows:

41. (Currently amended) An aqueous liquid preparation consisting

> essentially of the following two components, wherein the first component is 2-amino-3-(4bromobenzoyl) phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and the second component is tyloxapol ~~an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester~~, wherein said liquid preparation is formulated for ophthalmic administration, and wherein when a quaternary ammonium compound is included in said liquid preparation, the quaternary ammonium compound is limited to benzalkonium chloride.

Id., Response dated September 6, 2011.

The Applicants addressed the rejection of claim 41 under 35 U.S.C. § 103 over Yanni in view of Guy, alleging that Yanni did not disclose a composition of bromfenac and polysorbate 80. *Id.* "However [Yanni] does not disclose bromfenac, the acid, but an amide derivative thereof." *Id.* Further, Yanni teaches that bromfenac acids provoke ocular irritation, thereby teaching away from bromfenac acids. *Id.* The Applicants further alleged that Guy taught equivalency of tyloxapol and polysorbate 80 with steroids, not with a non-steroidal compound like tyloxapol. *Id.* "[O]ne skilled in the art would not have been motivated to combine the teachings of Yanni directed to nonsteroidal compositions with Guy directed to steroidal compositions." *Id.*

xiii) Notice of Allowance

A Notice of Allowance responsive to "the response to arguments submitted on September 6, 2011" was issued on December 23, 2011. *Id.*, Notice of Allowance dated December 23, 2011. *Id.* The Notice of Allowance was accompanied by an Examiner's Amendment, as follows:

> In claim 41, lines 3-4 after a hydrate thereof, insert -- wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate --.
>
> In claim 64, line 2-3 after a hydrate thereof, insert -- wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate --.

Id.

The Notice of Allowance was also accompanied by Reasons for Allowance, which stated:

> Applicants have found that tyloxapol is not equivalent to polysorbate 80 when combined with bromfenac. The present inventors have discovered that tyloxapol has an unexpected property in stabilizing an aqueous solution of bromfenac in comparison with polysorbate 80.

Id.

xiv) Inter Partes Review

A Petition for *Inter Partes* Review was submitted on June 26, 2014 by Metric, Inc. The Petitioner alleged, *inter alia*, that the claims of the '431 patent were obvious over U.S. Patent

Number 4,910,225 (Ogawa et al) in view of U.S. Patent Number 6,107,343 (Sallmann et al.). The review is pending as case number IPR2014-01041.

c) Prosecution History of U.S. Patent No. 8,497,304

The file history of related U.S. Patent No. 8,497,304 is attached as Exhibit 5. Application Serial No. 13/353,653 ("the '653 application") was filed as a division of Serial No. 10/525,006. The '653 application issued as U.S. Patent Number 8,497,304. The patent claims an aqueous liquid preparation comprising bromfenac and polyoxyl 40 stearate, instead of tyloxapol as claimed by the '290 patent. Therefore, the prosecution history of the '653 application is less relevant to the claim interpretation of the '290 patent and has been summarized briefly below.

i) Preliminary Amendments, Restriction and Election

The Applicants submitted two preliminary amendments, including new claims 19-27. In the second preliminary amendment dated February 15, 2012, original claim 1 was amended as follows:

> 1. (Currently amended) An aqueous liquid preparation comprising 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, provided that the alkyl aryl polyether alcohol type polymer is not tyloxapol.

Following a restriction requirement, the Applicants elected claims 1, 2, 4-14, 16 and 19-27 for prosecution, and polyethylene glycol fatty acid ester as a species for examination. *'653 Application Prosecution History, Response to Election filed April 3, 2012.*

ii) Office Action of August 30, 2012

The Examiner then rejected all of the claims under 35 U.S.C. § 103(a) as being unpatentable over Chen et al. (US 6383471). *Id., Office Action of August 30, 2012,* p. 4. The Examiner also rejected the claims as obvious over Sawa (US 5942508) in view of Chen et al. (US 6383471). In further combinations of prior art, the Examiner cited the following references: Sawa (US 6274592), Sawa (US 20010056098), Fukahori et al. (JP 402083323A), Gamache et al. (WO 01/15677), Yakuji Nippo Ltd. ("New Drugs in Japan: 2001", 2001 Edition, Published by May 11,2001, p.27-29), Aikawa et al. (JP 2002308764A).

iii) Response dated January 30, 2013 and Final rejection

Following the rejection, the Applicants amended claim 1 as follows:

> **1. (Currently amended)** An aqueous liquid preparation comprising 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a ~~pharmacologically acceptable~~ sodium salt thereof or a hydrate thereof, and ~~an alkyl aryl polyether alcohol type polymer or~~ a polyethylene glycol fatty acid ester, ~~provided that the alkyl aryl polyether alcohol type polymer is not Tyloxapol~~ wherein the concentration of the polyethylene glycol fatty acid ester is selected from a range of a minimum

concentration of 0.02 w/v % to a maximum concentration of 0.1 w/v%.

Id. Response dated January 30, 2013, p. 2. In their response, the Applicants alleged that there was unexpected stability by using Polyoxyl 40 stearate as compared to Polysorbate 80. *Id.* p. 8. However, the Examiner did not find the response persuasive and continued to reject the claims applying the same art. *See id. Final rejection dated May 10, 2013.*

iv) Response after Final and Notice of Allowance

In an after-final Response, the Applicants amended claim 1 as follows:

> 1. (Currently amended) An aqueous liquid preparation comprising 2-amino-3-(4-bromobenzoyl)phenylacetic acid ~~or a~~ sodium salt ~~thereof~~ or a hydrate thereof, and ~~a polyethylene glycol fatty acid ester~~ polyoxyl 40 stearate, wherein the concentration of the ~~polyethylene glycol fatty acid ester~~ polyoxyl 40 stearate is selected from a range of a minimum concentration of 0.02 w/v % to a maximum concentration of 0.1 w/v%.

Id. Response dated May 20, 2013, p. 2. The amendments were made in response to a suggestion by the Examiner. *Id.* p. 5. A Notice of Allowance as mailed on June 7, 2013. The claims issued as U.S. Patent No. 8,497,304 on July 30, 2013, with 0 days of Patent Term Adjustment.

d) Prosecution history of U.S. Patent 8,669,290

The prosecution history of U.S. Patent No. 8,669,290 ("the '290 patent") is attached as Exhibit 6. The '290 patent was filed as Application Serial Number 13/687,242 ("the '242 application"). The '242 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 November 28, 2012, in favor of new claims 19–48. *Prosecution History of the '290 patent*; Preliminary Amendment dated November 28, 2012. Independent claims 19, 26, and 32 as originally filed are presented below:

> 19. A stable aqueous liquid preparation comprising: (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 second component is tyloxapol and is present in said liquid preparation in an amount sufficient to stabilize said first component; and wherein said stable liquid preparation is formulated for ophthalmic administration.
>
> 26. A stable aqueous liquid preparation comprising: (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 second component is tyloxapol; wherein said stable liquid preparation is formulated for ophthalmic administration; and wherein the stable aqueous liquid preparation is characterized in that greater than about 90% of the original amount of the first component remains in the preparation after storage at about 60° C. for 4 weeks.

32. A stable aqueous liquid preparation comprising: (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 second component is tyloxapol; wherein said stable liquid preparation is formulated for ophthalmic administration; provided that the liquid preparation does not include mannitol.

Id.

ii) Office Action dated August 1, 2013

In an Office Action dated September 27, 2007, the Examiner rejected claims 19, 26, and 32 under 35 U.S.C. § 103(a) as being obvious over Gamache et al. (WO 01/15677 A2). *Id.*, Office Action dated August 1, 2013. The Examiner alleged that:

Gamache teaches compositions for otic and intranasal use…that contain a combination of a 5-HT agonist and an anti-inflammatory agent…or alternatively sequential or concurrent dosing of separate compositions that contain the 5-HT antagonist in one composition and the antiinflammatory agent in a second composition…; specifically claimed is the anti-inflammatory specie bromfenac… Typical concentrations of anti-inflammatory agents, such as bromfenac, are taught in the range 0.01-1.0 % (w/v) (overlapping with 0.01-0.5…); aqueous formulations are preferred…; tyloxapol is taught in a concentration of 0.05 % (w/v)…

Id.

Claims 19, 26, and 32 were rejected on the ground of nonstatutory double patenting as being unpatentable over:

claims 1-8 of U.S. Patent No. 7,829,544;

claims 1-22 of U.S. Patent No. 8,129,431;

claims 1-5 of copending Application No. 13/353653;

Id.

iii) Response dated October 22, 2013

A response dated October 22, 2013 was filed. *Id.*, Response dated October 22, 2013. In their response, the Applicants amended claims 19 and 32 as follows:

> 19. (Currently amended) A stable aqueous liquid preparation comprising: (a) a first component; and (b) a second component; wherein the first component is 2-amino-3-(4bromobenzoyl)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; and wherein said stable liquid preparation is formulated for ophthalmic administration.
>
> 32. (Currently amended) A stable aqueous liquid preparation comprising: (a) a first component; and (b) a second component; wherein the first component is 2-amino-3-(4bromobenzoyl)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.

Id.

The Applicants addressed the rejection of claims 19, 26, and 32 as being obvious over Gamache by arguing that claims 19, 27, and 32 recite that "the preparation comprises the first component, 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or anhydrate thereof (i.e. 'bromfenac'), as the sole pharmaceutical active ingredient contained in the preparation." *Id.* "Gamache does not teach or suggest any preparation comprising bromfenac as the sole pharmaceutical active ingredient. Gamache teaches only compositions that must contain 5-HT1D and/or 5-HT1B receptor agonists." *Id.*

The Applicants alleged that claim 26 recited that "greater than about 90% of the original amount of the first component [bromfenac] remains in the preparation after storage at about 60° C for 4 weeks."

> Gamache did not recognize the problem that bromfenac degrades rapidly in the presence of polysorbate 80, a surfactant 'known to those skilled in the art' (according to Gamache), as Applicant demonstrated in the grandparent application…Applicant recognized this problem and surprisingly found that the degradation of bromfenac could be avoided by specifically including tyloxapol in the preparation.

Id. The Applicants alleged that the preparation of claim 26 and its dependent claims was therefore not obvious from Gamache. *Id.*

The Applicants addressed the rejections on the ground of nonstatutory double patenting over claims of U.S. Patent Nos. 7,829,544 and 8,129,431, and U.S. Application Serial No. 13/353,653 by submitting a Terminal Disclaimer over all three. *Id.*

iv) Notice of Allowance

A Notice of Allowance was issued on January 15, 2014. *Id.*, Notice of Allowance. The Notice of Allowance was accompanied by an Examiner's Amendment. *Id.*

Claim 26 was amended in the Examiner's Amendment as follows:

> 26. A stable aqueous liquid preparation comprising: (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; and wherein the stable aqueous liquid preparation is characterized in that greater than about 90% of the original amount of the first component remains in the preparation after storage at about 60° C. for 4 weeks.

v) Inter Partes Review

A Petition for *Inter Partes* Review was submitted on June 26, 2014 by Metric, Inc. The Petitioner alleged, *inter alia*, that the claims of the '290 patent were obvious over U.S. Patent Number 4,910,225 (Ogawa et al) in view of U.S. Patent Number 6,107,343 (Sallmann et al.). The review is pending as case number IPR2014-01043.

C. INVALIDITY OF THE '131 PATENT

As explained in detail below, prior to the 102(b) date of the '131 patent (*i.e.*, January 16, 2003), a person of ordinary skill in the art would have found it obvious to prepare the claimed aqueous liquid preparation containing bromfenac. Further, such a person would have done so with a reasonable expectation of success.

1. Invalidity Analysis of the '131 Patent

Under 35 U.S.C. § 103(a), an applicant is not entitled to a patent "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious" to a person of ordinary skill in the art at the time the invention was made. 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 in *Graham* include:

(a) determining the scope and content 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.

Graham, 383 U.S. at 17-18.

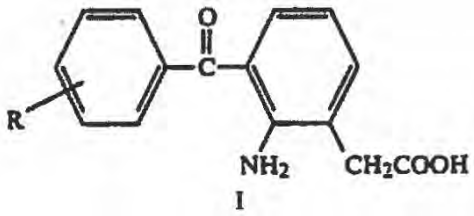
a) The Scope and Content of the Prior Art

i) U.S. Patent No. 4,910,225 to Ogawa et al.

U.S. Patent Number 4,910,225 ("the '225 patent") (Exhibit 7) was published on March 20, 1990, which is more than one year prior to the earliest priority date available to the '131 patent. Accordingly, the '225 patent is available as prior art under 35 U.S.C. § 102(b).

The '225 patent was disclosed to the USPTO during examination of the '131 patent but was not applied in any rejection against the claims. There can be "a heavy burden" in proving the invalidity of a patent using art disclosed to the PTO during the prosecution of the patent. *See Celeritas Technologies, Ltd. v. Rockwell International Corp.*, 150 F.3d 1354, 1360 (Fed. Cir. 1998), *citing Hewlett-Packard Co. v. Bausch & Lomb, Inc.* 909 F.2d 1464, 1467 (Fed. Cir. 1990). Despite this "heavy burden" the Federal Circuit has held patents invalid over the same prior art cited and applied by the USPTO, particularly where the Examiner did not fully appreciate the teachings of the prior art reference.

The '225 patent describes a "locally administrable therapeutic composition for inflammatory disease which is characterized by comprising benzoylphenylacetic acid" of formula I,



I

where R is a hydrogen or halogen atom, or a salt or hydrate thereof, as an active ingredient. *'225 patent*, Abstract. "An ophthalmic composition according to the invention can treat effectively inflammatory eye disease by topical application..." *Id.*

The ophthalmic compositions of the '225 patent can be prepared in "an aqueous base generally used in the production of ophthalmic preparations, for example sterile distilled water..." *Id.*, col. 3, ll. 39-43. "[T]he stability of an aqueous composition containing the above

compounds is remarkably enhanced by incorporating a water-soluble polymer and sulfite, and adjusting the pH to 6.0–9.0, preferably about 7.5–8.5…A water-soluble polymer includes polyvinyl pyrrolidone…" *Id.*, col. 3, ll. 48-58. "The pH adjustment is generally conducted with sodium hydroxide or hydrochloric acid, for instance, and it is advisable to form a buffer solution by combined use of, for example, sodium acetate, sodium borate or sodium phosphate and acetic acid, boric acid or phosphoric acid, respectively." *Id.*, col. 3, ll. 62-67.

A chelating agent, such as sodium edetate, may be added to the formulation. *Id.*, col. 4, ll. 21-35. 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 pH 8	**To make 100 ml**

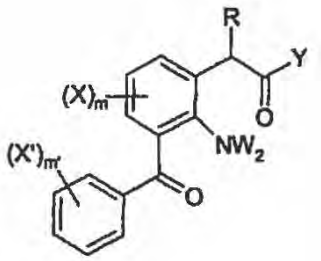
Id., Example 6. In the above Example 6, sodium 3-(4-bromobenzoyl)-2-aminophenyl-acetate monohydrate refers to the monohydrate of the sodium salt of bromfenac.

ii) WO 02/13804 to Kapin et al.

WO 02/13804 ("the '804 publication") (Exhibit 8) was published on February 21, 2002, which is more than one year prior to the effective U.S. filing date of the '131 patent. Accordingly, the '804 publication is available as prior art under 35 U.S.C. § 102(b).

The '804 publication was disclosed to the USPTO during examination of the '131 patent, however, was not applied in any rejection of the claims. Again, there can be "a heavy burden" in proving the invalidity of patent using art disclosed to the PTO during the prosecution of the patent. *Celeritas Technologies, Ltd. v. Rockwell International Corp.*, 150 F.3d 1354, 1360 (Fed. Cir. 1998).

The '804 publication recites topical or ophthalmic administration of 3-benzoylphenylacetic acids and derivatives thereof. *'804 publication*, Abstract; page 5, ll. 8-18. The 3-benzoylphenylacetic acids and derivatives thereof are compounds of Formula I:



(I)

where W may be H; m and m' are 0-3 and 0-5, respectively; X may be H; and X' may be halogen. *Id.*, Page 3. The compounds of Formula I may be acids (Y=—OH) or acid salts, or amides (Y=—NR_2). *Id.*

The '804 publication describes topical formulations comprising a compound of Formula I as the sole active ingredient; polysorbate 80; and benzalkonium chloride. *Id.*, Formulations 1 and 2 on pages 6-7. The '804 publication also describes a topical formulation comprising a derivative of 3-benzoylphenylacetic acid, i.e. nepafenac, as the sole active ingredient; tyloxapol; and benzalkonium chloride. *Id.*, Formulation 3 on page 7. Formulation 3 has the following constituents:

Formulation 3

Nepafenac	0.1 + 6% excess
Carbopol 974P	0.08%
Tyloxapol	0.01%
Glycerin	2.4%
Disodium EDTA	0.01%
Benzalkonium Chloride	0.01%
pH adjustment with NaOH and/or HCl	pH 7.5 ± 0.2
Water	q.s.100%

Id.

iii) U.S. Patent No. 5,414,011 to Fu et al.

U.S. Patent Number 5,414,011 ("the '011 patent") (Exhibit 9) was published on May 9, 1995, which is more than one year prior to the earliest filing date available to the '131 patent. Accordingly, the '011 patent is available as prior art under 35 U.S.C. 102(b).

The '011 patent was *not* considered by the USPTO during prosecution of the '131 patent. The Supreme Court has held that where the party challenging the validity of a patent presents prior art not found in the prosecution history of the patent and therefore not considered before the USPTO during examination of the application, "the challenger's burden... may be easier to sustain[.]" *Microsoft Corp. v. i4i L.P.* 131 S.Ct. 2238, 2251 (2011). While the challenger must

still prove invalidity by clear and convincing evidence, when "the PTO did not have all material facts before it, its considered judgment may lose significant force" and may therefore command less deference on the issue of validity. *Id.*

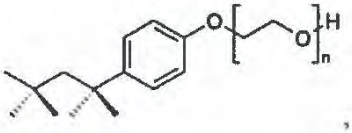
The '011 patent teaches stable, clear, antimicrobially effective ophthalmic formulations which included an NSAID, and a preservative system formed of a quaternary ammonium preservative and a nonionic polyoxyethylated octylphenol surfactant, all in an aqueous vehicle. *'011 patent, Abstract.* "The preservative system can be used with other formulations which require the preservative to be ophthalmologically acceptable and antimicrobially effective." *Id.*

The preservative system purports to solves the prior art problem of non-steroidal anti-inflammatory drugs (NSAIDs) being "incompatible with quaternary ammonium compounds, such as benzalkonium chloride (BAC), because NSAIDs can form a complex with BAC, rendering the preservative less available to serve its function, as is the case with other ophthalmic drugs that contain a --COOH group." *'011 patent*, col. 2, ll. 48-53. Alternative quaternary ammonium compounds may include cetyltrimethylammonium bromide (CTAB). *See id.* col. 6, ll. 23-26. The preferred formulations contain NSAID, BAC, octoxynol 40, EDTA disodium, NaCl, and NaOH or HCl in purified water. *Id. col. 7, ll. 38-50.*

The '011 patent defines the term "stabilizing" to mean "keeping a formulation clear and antimicrobially effective for its minimum reasonable shelf life, e.g., at least one year." *Id.*, col. 4, ll. 15-18. "Formulations using surfactants other than the nonionic surfactants of the invention did not remain clear and were not stable." *Id.*, col. 12, ll. 26-30. The '011 patent does not describe what these other surfactants are. However, the '011 patent does list a number of prior art patents. The surfactants for use in BAC containing solutions described in these patents are listed below:

Patent No.	NSAID	Surfactant
4,454,151	5-benzoyl-1,2-dihydro-3H-pyrrolo(1,2-a)-pyrrole-1-carboxylic acid	Polysorbate 80
4,607,038	Pranoprofen	polyoxyethylenesorbitan monooleate, polyoxyethyleneoxystearic acid triglyceride, polyethylene glycol

The preferred nonionic surfactants include Octoxynol 10 and most preferably Octoxynol 40 which is a nonionic surfactant material. *Id.* col. 6, ll. 27-40. The structure of Octoxynol 10 and 40 are reproduced below:



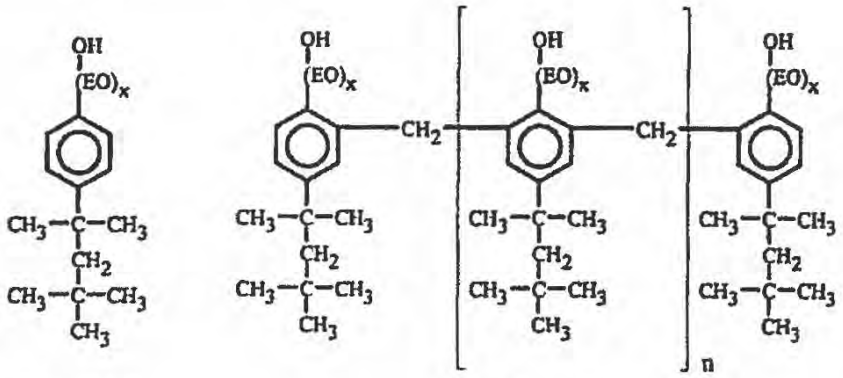
where n = 10 or 40. Specific formulations contain NSAID, BAC (0.01 w/v%) and Octoxynol 40 (0.02 w/v%). *See id.*, Examples 2 and 7.

iv) Regev and Zana, Journal of Colloid and Interface Science (210) 8–17 (1999).

Regev and Zana, *Journal of Colloid and Interface Science* (210) 8–17 (1999) ("Regev") (Exhibit 10) was published in 1999, which is more than one year prior to the earliest filing date available to the '131 patent. Accordingly, Regev is available as prior art under 35 U.S.C. § 102(b).

Regev was *not* considered by the USPTO during prosecution of the '131 patent. The Supreme Court has held that where the party challenging the validity of a patent presents prior art not considered before the USPTO during examination of the application, courts have held that "the challenger's burden . . . may be easier to sustain[.]" *Microsoft Corp. v. i4i L.P.* 131 S.Ct. 2238, 2251 (2011). When "the PTO did not have all material facts before it, its considered judgment may lose significant force" and may therefore command less deference on the issue of validity. *Id.*

Regev teaches that tyloxapol is a nonionic surfactant based on an oligomer of 4-(1,1,3,3-tetramethylbutyl)phenol and formaldehyde. *Regev, Scheme 1, reproduced below*. The phenolic groups in the oligomer are ethoxylated. *Id.*



Triton X-100 Tyloxapol

x = 9-10 x = 8-10 n < 6

SCHEME 1. Chemical structures of Triton X-100 and of Tyloxapol (EO= $-CH_2CH_2O-$).

Regev further teaches that Tyloxapol is "very close to being an oligomer of the much investigated Triton X-100." *Regev*, page 8. The oligomeric surfactant tyloxapol has a cloud point of 90 ± 1°C, while the monomeric surfactant Triton X-100 has a cloud point of 65.9 ± 0.2°C. *Id.*, page 9. Below the cloud point, a micellar solution exists; above the cloud point, the surfactant

loses water solubility and a cloudy dispersion exists.[9] Regev also teaches that the cmc range of TX-100 is "seen to be around 0.01 wt%, i.e., 0.15 mM." *Id.*, page 11. Regev reports the cmc range of tyloxapol may be 1.6 micromolar (0.0016 mM). *Id.* "[I]onic surfactant oligomers have consistently been found to have much lower cmc values than the corresponding monomers. A similar behavior is expected for Tyloxapol with respect to TX100." *Id.* page 12. Tyloxapol micelles provide a hydrophobic solute, such as pyrene, a less polar, or more hydrophobic, environment than TX100 micelles. *Id.*

v) Yuan et al., J. Phys. Chem. B, 2001, 105, 4611-4615

Yuan et al., *J. Phys. Chem. B* 2001, 105, 4611-4615 ("Yuan") (Exhibit 11) was published in 1999, which is more than one year prior to the earliest filing date available to the '131 patent. Accordingly, Yuan is available as prior art under 35 U.S.C. § 102(b).

Yuan was *not* considered by the USPTO during prosecution of the '131 patent. The Supreme Court has held that where the party challenging the validity of a patent presents prior art not considered before the USPTO during examination of the application, courts have held that "the challenger's burden . . . may be easier to sustain[.]" *Microsoft Corp. v. i4i L.P.* 131 S.Ct. 2238, 2251 (2011). When "the PTO did not have all material facts before it, its considered judgment may lose significant force" and may therefore command less deference on the issue of validity. *Id.*

Yuan describes the structure of a mixed micelle formed from an ethoxylated 4-(1,1,3,3tetramethylbutyl)phenol surfactant (Triton X-100); 9 moles ethylene oxide:1 mole phenol) and cetyltrimethylammonium bromide (CTAB). *Yuan*, Abstract. The methyl groups attached to the cationic nitrogen atom of CTAB are located between oxyethylene groups bound to the phenolic –OH groups of the alkylphenol moiety of Triton X-100. *Id.* The $-CH_2-$ group of the cetyl moiety bound to the cationic nitrogen atom of CTAB is near the phenoxy ring of Triton X-100. *Id.*, page 4614. The polyoxyethylene chain of Triton X-100 is closely packed outside the hydrophobic micelle core. *Id.*, Abstract. Intermolecular interaction between Triton X-100 molecules weakens as the concentration of CTAB increases. *Id.*, page 4615.

vi) U.S. Patent Number 2,454,541 to Bock et al.

U.S. Patent Number 2,454,541 ("the '541 patent") (Exhibit 12) was published on November 23, 1948, which is more than one year prior to the earliest filing date available to the '131 patent. Accordingly, the '541 patent is available as prior art under 35 U.S.C. § 102(b).

The '541 patent was *not* considered by the USPTO during prosecution of the '131 patent. The Supreme Court has held that where the party challenging the validity of a patent presents prior art not found in the prosecution history of the patent and therefore not considered before the USPTO during examination of the application, "the challenger's burden . . . may be easier to sustain[.]" *Microsoft Corp. v. i4i L.P.* 131 S.Ct. 2238, 2251 (2011). While the challenger must

[9] Alauddin et al. "Effect of Organic Additives on the Cloud Point of Triton X-100 Micelles." *Journal of Applied Sciences, 9: 2301-2306 (2009).*

still prove invalidity by clear and convincing evidence, when "the PTO did not have all material facts before it, its considered judgment may lose significant force" and may therefore command less deference on the issue of validity. *Id.*

The '541 patent describes polymeric surfactants made by reacting an alkylphenol and formaldehyde to obtain a phenol-formaldehyde product, and then ethoxylating the phenol-formaldehyde product. *'541 patent*, Example 1; claim 1. The '541 patent teaches that conventional surfactants lose micellar structure in response to changes in concentration of the surfactant or salts, or changes in temperature. *Id.*, col. 1, ll. 35-52. The ethoxylated phenol-formaldehyde surfactants of the '541 patent "is in fact a macromolecule which imparts capillary- or surface-activity to a solution, as do micelles of ordinary soaps, but which is stable and is not dissociated as are the micelles of ordinary detergents under adverse conditions." *Id.*, col. 2, ll. 44-51.

b) Claim Interpretation

i) Interpretation of Independent Claims 1 and 13

In order to ascertain the true meaning of claims, it is appropriate to consider the claim language, the patent specification, and the prosecution history. Claim terms are given their ordinary and customary meaning unless examination of the specification, prosecution history, and other claims indicates that the applicant intended otherwise.

Claim 1 of the '131 patent purports to recite an aqueous liquid preparation comprising:

> 2-amino-3-(4-bromobenzoyl)phenylacetic acid (bromfenac), a pharmacologically acceptable salt thereof, or a hydrate thereof (a first component); and
>
> tyloxapol (a second component).

The hydrate is at least one of a hemihydrate (1/2 hydrate); a monohydrate; and a sesquihydrate (3/2 hydrate). The liquid preparation of claim 1 is formulated for ophthalmic administration.

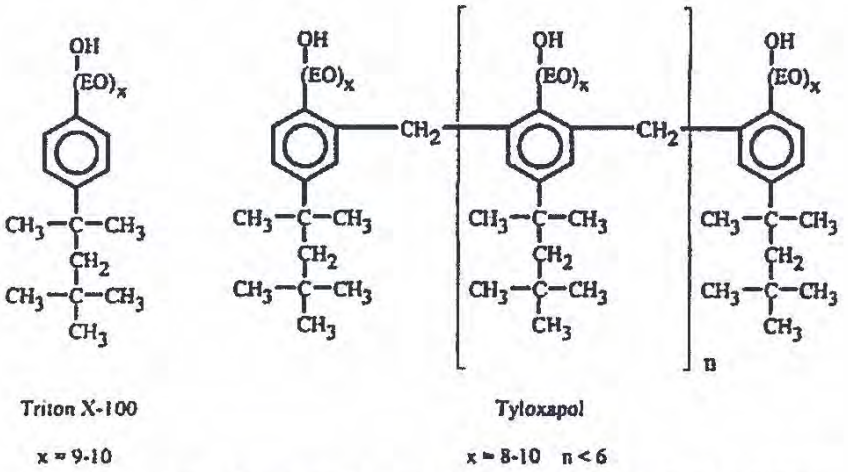
Bromfenac is the sole pharmaceutical active ingredient contained in the preparation, and is present in the preparation at a concentration from about 0.05 w/v % to about 0.2 w/v %. Tyloxapol is present in the liquid preparation in an amount sufficient to stabilize bromfenac. The stable liquid preparation is formulated for ophthalmic administration.

The specification defines tyloxapol as an alkyl aryl polyether alcohol type polymer. *'131 patent, Abstract.*

The specification describes benzalkonium chloride as a quaternary ammonium compound having a preservative effect. *Id., col. 2, ll. 4-10.*

The formulation of claim 1 may, purportedly, additionally contain one or more additives selected from the group consisting of a buffer, thickener, stabilizer, chelating agent, and pH controlling agent. *Id., claim 30.*

The ordinary meaning of the term tyloxapol is a nonionic surfactant based on an oligomer of 4-(1,1,3,3-tetramethylbutyl)phenol and formaldehyde. *Regev, Scheme 1, reproduced below.* The phenolic groups in the oligomer are ethoxylated. *Id.*



Triton X-100 Tyloxapol

x = 9-10 x = 8-10 n < 6

SCHEME 1. Chemical structures of Triton X-100 and of Tyloxapol (EO= $-CH_2CH_2O-$).

Claim 13 is substantially similar to claim 1, except that it adds the further limitation that the liquid preparation *does not include mannitol*, and does not recite that tyloxapol is present in an amount effective to stabilize bromfenac.

Accordingly, claim 1 requires an aqueous liquid preparation comprising bromfenac; tyloxapol in an amount sufficient to stabilize bromfenac; and optionally various biologically inactive additives. Claim 1 excludes active ingredients other than bromfenac.

d) Obviousness of Claims 1 and 13 In Light of the '804 Publication, the '011 Patent and Regev

i) Scope and Content of the Prior Art

The scope and content of the prior art is discussed above and is, therefore, not repeated here.

ii) Level of Ordinary Skill in the Art

The level of ordinary skill in the art is high. The person of ordinary skill in the art has an advanced degree in organic chemistry, medicinal chemistry, and/or pharmacy. Additionally, the

person of ordinary skill would have experience in developing topical formulations containing surfactants and antimicrobial additives. Furthermore, the person of ordinary skill would be aware of the above cited prior art references as commonly directed to NSAID-containing ophthalmic formulations including suitable additives, such as nonionic surfactants, as well as references describe the known properties of such surfactants. The education and work experience of the person of ordinary skill would also be exemplified by the qualifications of the inventors and authors of the above cited prior art.

iii) Differences Between the Art and the Claims

As discussed above, the '225 patent discloses, in Example 6, an ophthalmic formulation containing the following ingredients:

EXAMPLE 6

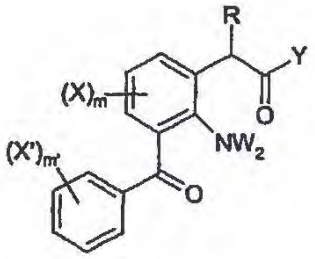
Ophthalmic Solution

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	

Id., Example 6.

Accordingly, Example 6 of the '225 patent describes an aqueous liquid preparation comprising the *monohydrate of the sodium salt of bromfenac* (100 mg/100 mL, or *0.1 % w/v*); polysorbate 80; benzalkonium chloride, and various biologically inactive additives (not including mannitol). Example 6 does not include active ingredients other than bromfenac. *The only difference between Example 6 of the '225 patent and claims 1 and 13 of the '131 patent is the nonionic surfactant, i.e. polysorbate 80 rather than tyloxapol.* The '131 patent alleges that the use of tyloxapol instead of polysorbate 80 *surprisingly and significantly improves the stability of the formulation.*

However, before the filing of the '131 patent, tyloxapol was a well known nonionic surfactant for use in ophthalmic solutions. For example, the '804 publication describes topical or ophthalmic administration of 3-benzoylphenylacetic acids and derivatives thereof. *'804 publication*, Abstract; page 5, ll. 8-18. The 3-benzoylphenylacetic acids and derivatives thereof are compounds of Formula I:



(I)

which include bromfenac when R=H, Y is OR', R'=H, X'=Br, m=0, m'=1, and W=H. *Id.* p. 3.

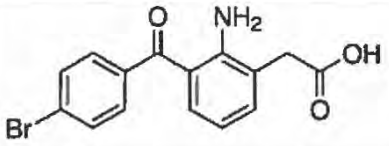
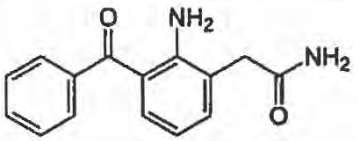
The '804 publication describes topical formulations comprising a compound of Formula I as the sole active ingredient; polysorbate 80; and benzalkonium chloride. *Id.*, Formulations 1 and 2 on pages 6-7. *The difference between these formulations and that of claim 1 of the '131 patent again is the presence of polysorbate 80 instead of tyloxapol.*

The '804 publication also describes a topical formulation comprising a derivative of 3-benzoylphenylacetic acid, nepafenac (0.1 %), as the sole active ingredient; tyloxapol; and benzalkonium chloride. *Id.*, Formulation 3 on page 7. Formulation 3 has the following constituents:

Formulation 3

Nepafenac	0.1 + 6% excess
Carbopol 974P	0.08%
Tyloxapol	0.01%
Glycerin	2.4%
Disodium EDTA	0.01%
Benzalkonium Chloride	0.01%
pH adjustment with NaOH and/or HCl	pH 7.5 ± 0.2
Water	q.s.100%

Id. The difference between this formulation and that of claim 1 of the '131 patent is the presence of nepafenac instead of bromfenac. Nepafenac differs from bromfenac in the absence of a bromine substitution and the presence of an acetamide rather than the carboxylic acid as shown below:

Bromfenac	Nepafenac
	

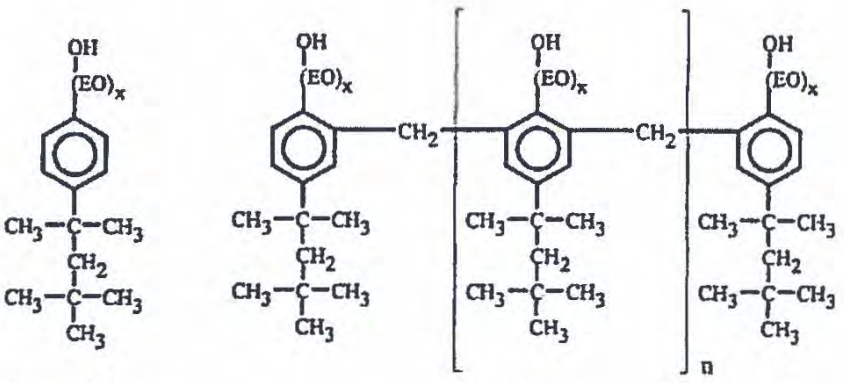
While the '804 publication does not teach the express combination of tyloxapol and bromfenac, it does teach the suitability of tyloxapol in NSAID ophthalmic formulations, including for compounds very similar to bromfenac. The formulations of the '225 patent and the '804 publication do not include mannitol, and therefore meet the negative limitation of claim 13.

iv) Motivation to Combine the References

The '804 publication teaches the substitutability of tyloxapol for polysorbate 80 as a surfactant for aqueous ophthalmic solutions, including bromfenac generically. However, neither the '225 patent nor the '804 publication teach any impact on stability in the choice of surfactant. The Examples of the '225 patent and the '804 publication each contain benzalkonium chloride.

It was known at the relevant time that a nonionic surfactant was important for stabilizing an aqueous solution of an NSAID and benzalkonium chloride. The '011 patent describes "a formulation containing an ophthalmologically effective amount of an NSAID alone or in combination with an antibiotic, a quaternary ammonium preservative and a stabilizing amount of a nonionic polyoxyethylated octylphenol surfactant, all in an aqueous vehicle." *'011 patent*, col. 2, line 66-col. 3, line 4. The preservative system solves the problem of NSAIDs forming a complex with BAC, rendering the preservative less available to serve its function. *Id.*, col. 2, ll. 48-53. "Formulations using surfactants other than the nonionic surfactants of the invention did not remain clear *and were not stable*." *Id.*, col. 12, ll. 26-30. The preferred surfactants of the '011 patent include octoxynol-10 and -40. In view of the '011 patent, a person of ordinary skill would have considered polyoxyethylated octylphenol surfactants, including octoxynol-10 and -40, as preferred surfactants for improving the stability of NSAIDs in aqueous solutions containing BAC.

The similarities between monomeric octoxynol polyoxyethylated octylphenol surfactants and Tyloxapol were also known prior to the filing of the '131 patent. For example, "Tyloxapol is very close to being an oligomer of the much investigated Triton X-100." *Regev*, page 8. According to Regev, Triton X-100 is a monomeric nonionic polyoxyethylated octylphenol surfactant, specifically octoxynol-9 and octoxynol-10 (disclosed in the '011 patent).



SCHEME 1. Chemical structures of Triton X-100 and of Tyloxapol (EO= $-CH_2CH_2O-$).

The oligomeric surfactant tyloxapol has a cloud point of 90 ± 1°C, higher than that of the monomeric surfactant Triton X-100 which has a cloud point of 65.9 ± 0.2°C. *Id.*, page 9. Below the cloud point, a micellar solution exists; above the cloud point, the surfactant loses water solubility and a cloudy dispersion exists.[10] Furthermore, the cmc range of TX-100 is 0.15 mM, as compared to the cmc range of tyloxapol of 1.6 micromolar (0.0016 mM). *Id.*, page 11. Tyloxapol is thus a surfactant with a lower critical micelle concentration than that of TX-100. "[I]onic surfactant oligomers have consistently been found to have much lower cmc values than the corresponding monomers. A similar behavior is expected for Tyloxapol with respect to TX100." *Id.*, page 12. Since tyloxapol has a higher cloud point and a lower critical micelle concentration than the corresponding monomeric nonionic polyoxyethylated octylphenol surfactant, a person of ordinary skill would have expected tyloxapol formulations to remain clear over a wider temperature range

In view of Regev, the person of ordinary skill in the art would have been motivated to modify the mannitol-free formulation of Example 6 of the '225 patent, as modified by the '011 patent, to use the ethoxylated octylphenol oligomer tyloxapol as the nonionic polyoxyethylated octylphenol surfactant. A person of ordinary skill would have expected tyloxapol formulations to remain clear over a wider temperature range. A reasonable expectation of success is shown in the teachings of the '804 publication that tyloxapol may be substituted for polysorbate 80 in topical or ophthalmic administration of 3-benzoylphenylacetic acids and derivatives thereof which contain benzalkonium chloride.

Since a person of ordinary skill in the art would have been motivated in view of the '804 publication, the '011 patent and Regev to replace polysorbate 80 with tyloxapol, the combination

[10] Alauddin et al. "Effect of Organic Additives on the Cloud Point of Triton X-100 Micelles." *Journal of Applied Sciences, 9: 2301-2306 (2009).*

of the prior art teaches all of the elements of claims 1 and 13. Thus, claims 1 and 13 would have been *prima facie* obvious over the prior art.

e) Obviousness of Claims 1 and 13 In Light of the '804 Publication, the '011 Patent, Yuan, and the '541 Patent

i) Scope and Content of the Prior Art

The scope and content of the prior art is discussed above and is, therefore, not repeated here.

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

The formulation of Example 6 of the '225 patent differs from the formulation of claims 1 and 13 in that it contains the nonionic surfactant polysorbate 80 rather than the nonionic surfactant tyloxapol.

As discussed above, the '804 publication describes topical formulations comprising a 3-benzoylphenylacetic acid or a derivative thereof as the sole active ingredient; polysorbate 80; and benzalkonium chloride. *Id.*, Formulations 1 and 2 on pages 6-7. These formulations do not include tyloxapol. 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. *Id.*, Formulation 3 on page 7. This formulation does not contain bromfenac. However, through these examples, the '804 publication suggests that tyloxapol may be substituted for polysorbate 80.

iv) Motivation to Combine the References

The '011 patent teaches that a preservative system for stabilizing ophthalmic aqueous solutions containing NSAIDs. The preservative system includes a quaternary ammonium preservative and polyoxyethylated octylphenol surfactant that solves the known incompatibility of NSAIDs and quaternary ammonium compounds, such as benzalkonium chloride (BAC), where NSAIDs can form a complex with BAC, rendering the preservative less available to serve its function. *'011 patent*, col. 2, ll. 48-53. The '011 patent defines the term "stabilizing" to mean "keeping a formulation clear and antimicrobially effective for its minimum reasonable shelf life, e.g., at least one year." *Id.*, col. 4, ll. 16-18. "Formulations using surfactants other than the nonionic surfactants of the invention did not remain clear and were not stable." *Id.*, col. 12, ll. 26-30. In view of the '011 patent, a person of ordinary skill would have considered polyoxyethylated octylphenol surfactants, including octoxynol-10 and -40 as preferred surfactants for improving the stability of NSAIDs in aqueous solutions containing BAC or CTAB.

Yuan provides an explanation for stabilization of NSAID/quaternary ammonium aqueous solutions by polyoxyethylated octylphenol surfactants, as described by the '011 patent. In particular, Yuan teaches that quaternary ammonium compounds, such as CTAB, and polyoxyethylated octylphenol surfactants, such as Triton X-100, form mixed micelles. *Yuan*, Abstract. CTAB was a known alternative to BAC for use as quaternary ammonium preservative. *See the '011 patent, col. 6, ll. 23-26.* The cationic nitrogen atom of a quaternary ammonium compound is located between oxyethylene groups bound to the phenolic –OH groups of a polyoxyethylated octylphenol surfactant. *Yuan*, page 4614. The polyoxyethylene chains of the polyoxyethylated octylphenol surfactant are closely packed outside the hydrophobic micelle core, thereby embedding cationic nitrogen atoms in a polyoxyethylene layer. *Id.*

Moreover, the '541 patent teaches that conventional surfactants lose micellar structure in response to changes in concentration or changes in temperature, while ethoxylated phenol-formaldehyde surfactants, *e.g.*, tyloxapol, "[are] stable and [are] not dissociated as are the micelles of ordinary detergents under adverse conditions." *'541 patent*, col. 2, ll. 44-51. More specifically, the ethoxylated phenol-formaldehyde surfactant of the '541 patent "is in fact a macromolecule which imparts capillary- or surface-activity to a solution, as do micelles of ordinary soaps, but which is stable and is not dissociated as are the micelles of ordinary detergents under adverse conditions." *Id.*, col. 2, ll. 44-51.

A person of ordinary skill in the art would have been motivated to modify the formulation of Example 6 of the '225 patent, in view of the '011 patent and Yuan, to use the ethoxylated octylphenol oligomer tyloxapol as the nonionic polyoxyethylated octylphenol surfactant, as suggested by the '804 publication. Motivation to do so is found in the teachings of the '541 patent that conventional surfactants lose micellar structure in response to changes in concentration or changes in temperature, while ethoxylated phenol-formaldehyde surfactants, *e.g.*, tyloxapol, "[are] stable and [are] not dissociated as are the micelles of ordinary detergents under adverse conditions." *'541 patent*, col. 2, ll. 44-51.

Since a person of ordinary skill in the art would have been motivated in view of the '804 publication, the '011 Patent, Yuan, and the '541 patent to replace polysorbate 80 with tyloxapol, such a combination of the prior art teaches all of the elements of claims 1 and 13. Thus, claims 1 and 13 would have been *prima facie* obvious over the prior art.

f) Obviousness of Independent Claim 7

Claim 7 recites a stable aqueous liquid preparation comprising:

> (a) a first component, wherein the first component is bromfenac 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; and
>
> (b) a second component, where the second component is tyloxapol;
>
> wherein said stable liquid preparation is formulated for ophthalmic administration.

Bromfenac is the sole pharmaceutical active ingredient contained in the preparation, and is present in the preparation at a concentration from about 0.05 w/v % to about 0.2 w/v %. The stable aqueous liquid preparation 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.

The scope of claim 7 is substantially similar to claim 1, except that claim 7 recites that the stable aqueous liquid preparation is characterized in that greater than about 90% of the original amount of the first component remains in the preparation after storage at about 60° C. for 4 weeks. Claim 7 does not include the limitation of claim 1 that tyloxapol is present in an amount effective to stabilize the first component.

Accordingly, claim 7 is properly interpreted to require an aqueous liquid preparation comprising about 0.05 w/v % to about 0.2 w/v % bromfenac; tyloxapol; and optionally various biologically inactive additives. Claim 7 excludes active ingredients other than bromfenac. Claim 7 further requires that greater than about 90% of the original amount of bromfenac remains in the preparation after storage at about 60° C for 4 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. This formulation contains:

0.1 g bromfenac/100 ml (1 mg/ml); and

0.15 g polysorbate 80/100 ml (1.5 mg/ml).

Since the density of 1 ml of a dilute aqueous solution is ~1.0 g/ml, the formulation of Example 6 contains:

1 mg bromfenac/1000 mg solution, or 0.1 w/v% bromfenac; and

1.5 mg polysorbate 80/1000 mg solution, or 0.15 w/v% polysorbate 80.

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.*

As discussed above with regard to claim 1, a person of ordinary skill in the art would have been motivated by the teachings of the '804 publication, the '011 patent and Regev to replace polysorbate 80 with tyloxapol in the formulation of Example 6 of the '225 patent. As further discussed with regard to claim 1, a person of ordinary skill would have been motivated in view of the '804 publication, the '011 Patent, Yuan, and the '541 patent to replace polysorbate 80 with tyloxapol in the formulation of Example 6 of the '225 patent. Accordingly, the combination of ingredients in the formulation of claim 7 is obvious over the '225 patent in view of the '804 publication, the '011 patent, and Regev; and over the '225 patent in view of the '804 publication, the '011 Patent, Yuan, and the '541 patent.

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. 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 of claim 7 is obvious over the '225 patent in view of the '804 publication, the '011 patent, and Regev; and over the '225 patent in view of the '804 publication, the '011 Patent, Yuan, and the '541 patent. Claim 8 further limits the formulation 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, claim 7 is 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.

g) Secondary Considerations

In the specification of the '131 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. *'131 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 '131 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 May 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 '131 patent. Therefore, commercial success, if any, would not overcome the *prima facie* case of obviousness set forth above.

h) Obviousness of Claims 2, 8 and 14: Quaternary Ammonium Salt

Claims 2, 8, and 14 depend from claims 1, 7, and 13, respectively, and further limit their respective base claims by reciting that the composition further comprises a quaternary ammonium salt. Based on the above analysis of claims 1, 7, and 13, claims 2, 8 and 14 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.

Benzalkonium chloride is defined in the specification of the '131 patent as a quaternary ammonium salt. *'131 patent*, col. 2, ll. 23-29.

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 claim 2. *'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. *Id.*, Formulation 3 on page 7.

The '011 patent teaches a formulation containing an ophthalmologically effective amount of an NSAID in combination with "a preservative system formed of a quaternary ammonium preservative and a nonionic polyoxyethylated octylphenol surfactant, all in an aqueous vehicle." *Id.*, Abstract.

Accordingly, the prior art teaches use of quaternary ammonium compounds in aqueous formulations of 3-benzoylphenyl acetic acid NSAIDs, including bromfenac, and nonionic polyoxyethylated octylphenol surfactants. Therefore, claims 2, 8, and 14 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.

i) Obviousness of Claims 3 and 15: Bromfenac Sodium Salt

Claims 3 and 15 depend from claims 1 and 13, respectively, and further limit their respective base claims by reciting that the first component in the composition is a 2-amino-3-(4-bromobenzoyl)phenylacetic acid (bromfenac) sodium salt. Based on th above analysis of claims 1 and 13, claims 3 and 15 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.

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 3 and 15. *'225 patent*, Example 6.

Accordingly, claims 3 and 15 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.

j) Obviousness of Claim 4: Amount of Tyloxapol

Claim 4 depends from claim 1, and further limits claim 1 by reciting that the concentration of tyloxapol is from about 0.01 w/v % to about 0.05 w/v %.

As discussed above, claim 1 is 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.

Example 6 of the '225 patent describes an aqueous liquid preparation comprising the monohydrate of the sodium salt of bromfenac; polysorbate 80 (0.15 % w/v); benzalkonium chloride, and various biologically inactive additives.

The '804 publication also describes a topical formulation comprising a derivative of 3-benzoylphenylacetic acid, as the sole active ingredient; polysorbate 80 (0.01 w/v%); 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 (0.01 w/v%); and benzalkonium chloride. *'804 publication*, Formulation 3 on page 7.

Accordingly, the '804 publication teaches that tyloxapol and polysorbate 80 may each be used at a concentration of 0.01 % w/v. Furthermore, the cmc range of TX-100 is 0.15 mM, as compared to the cmc range of tyloxapol of 1.6 micromolar (0.0016 mM). *Regev*, page 11. "The aggregation behavior of the nonionic surfactant oligomer Tyloxapol has been investigated and compared to that of its corresponding monomer, Triton X-100, in water. It has been found that aggregates that can shield pyrene from water are present in Tyloxapol solutions at a concentration about 100-fold lower than for TX100." *Id.*, page 17.

As such, it would have been 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% with 0.01 w/v% of tyloxapol, as encompassed by claim 3. The person of ordinary skill would have a reasonable likelihood of success in making this modification, since the '804 publication teaches that tyloxapol and polysorbate 80 are each effective at a concentration of 0.01 % w/v.; and Regev teaches that tyloxapol may be used in a lower concentration than polysorbate 80, due to its lower critical micelle concentration.

Therefore, claim 4 is 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.

k) Obviousness of Claims 5, 11 and 17: pH From About 7.5 To About 8.5

Claims 5, 11, and 17 depend from claims 1, 7, and 13, respectively, and further limit their respective base claims by reciting that the pH of the aqueous liquid preparation is from about 7.5 to about 8.5. As discussed above, claims 1, 7, and 13 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 formulation of Example 6 of the '225 patent has a pH of 8, as encompassed by claims 5, 11, and 17. *'225 patent*, Example 5.

The formulation of Formulation 3 of the '804 publication has a pH of 7.5, as encompassed by claims 5, 11, and 17. *'804 publication*, Formulation 3.

Accordingly, a person of ordinary skill in the art would have found it obvious to prepare the formulation of any of claims 1, 7, and 13 at a pH of between 7.5 and 8.

Therefore, claims 5, 11 and 17 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.

l) Obviousness of Clams 6, 12, 18 and 24: Specific Formualtions

Claims 6 and 12 depend from claims 1 and 7, respectively, and further limit their base claims by reciting that the formulation consists essentially of:

bromfenac sodium salt;[11]

tyloxapol;

boric acid;

sodium tetraborate;

EDTA sodium salt;

benzalkonium chloride;

polyvinyl pyrrolidone; and

sodium sulfite.

Claims 18 and 24 each depend from claim 13. Claims 18, and 24 each further limit claim 13 by reciting that the formulation of claim 13 consists essentially of:

bromfenac sodium salt;[6]

tyloxapol;

boric acid;

sodium tetraborate;

EDTA sodium salt;

benzalkonium chloride;

polyvinyl pyrrolidone; and

sodium sulfite.

The liquid preparation of claims 6, 12, 18, and 24 is formulated for ophthalmic administration.[12]

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[11] Claims 12, 18, and 24 recite bromfenac, a pharmacologically acceptable salt thereof, or a hydrate thereof as component (a); however, later in the claim, a concentration of bromfenac sodium salt is defined. Accordingly, these claims require bromfenac sodium salt.

The formulation of claim 6 contains tyloxapol at a concentration of about 0.01 w/v % to about 0.05 w/v %; and bromfenac sodium salt at a concentration of about 0.02 w/v % to about 0.1 w/v %.

The formulation of claim 12 contains tyloxapol at a concentration of about 0.02 w/v %; and bromfenac sodium salt at a concentration of about 0.05 w/v % to about 0.1 w/v %.

The formulation of claim 18 contains tyloxapol at a concentration of about 0.02 w/v % to about 0.05 w/v %; and bromfenac sodium salt at a concentration of about 0.02 w/v % to about 0.1 w/v %.

The formulation of claim 24 contains bromfenac sodium salt at a concentration of about 0.05 w/v % to about 0.1 w/v %.

Accordingly, claims 6 and 24 each encompass a formulation containing *tyloxapol at a concentration of about 0.01 w/v % to about 0.05 w/v %;* and *bromfenac sodium salt at a concentration of about 0.05 w/v % to about 0.1 w/v %.*

Further, claims 12 and 18 each encompasses a formulation containing *tyloxapol at a concentration of about 0.02 w/v %*; and *bromfenac sodium salt at a concentration of about 0.05 w/v % to about 0.1 w/v %.*

Claims 6, 12, 18, and 24 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.

Accordingly, claims 6, 12, 18, and 24 are properly interpreted to require an aqueous liquid preparation consisting essentially of bromfenac; tyloxapol; boric acid; sodium tetraborate

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[12] This limitation is only explicitly recited in claims 6 and 24. However, claims 12 and 18 inherit this limitation from their respective base claims, claims 7 and 13.

(borax); EDTA sodium salt (edetate sodium salt); benzalkonium chloride; polyvinylpyrrolidone; and sodium sulfite. Claims 6, 12, 18, and 24 exclude active ingredients other than bromfenac.

As discussed above, claims 1, 7, and 13 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. All ingredients and limitations required by claims 6, 12, 18, and 24 are shown by Example 6 of the '225 patent, the only difference being the use of polysorbate in a concentration of 0.15 w/v % instead of tyloxapol at a concentration of about 0.02 w/v %, or about 0.01 w/v % to about 0.05 w/v %.

In Example 6 of the '225 patent, defined as an ophthalmic solution, bromfenac sodium salt, monohydrate, is used as the sole active ingredient in an amount of 100 mg/100 ml, or 0.1 % w/v, as encompassed by claims 6, 12, 18, and 24.

As discussed above with regard to claim 4, the '804 publication describes a topical formulation comprising a derivative of 3-benzoylphenylacetic acid, as the sole active ingredient; polysorbate 80 (0.01 w/v%); 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 (0.01 w/v %); and benzalkonium chloride. *'804 publication*, Formulation 3 on page 7.

Accordingly, it would have been 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 % with 0.01 w/v% of tyloxapol. The person of ordinary skill would have a reasonable likelihood of success in making this modification, since the '804 publication teaches that tyloxapol and polysorbate 80 are each effective at a concentration of 0.01 % w/v.; and Regev teaches that tyloxapol may be used in a lower concentration than polysorbate 80, due to its lower critical micelle concentration.

Tyloxapol in a concentration of 0.01 w/v% is encompassed by claim 6. Claim 24 does not require a specific concentration of tyloxapol. Accordingly, claims 6 and 24 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.

m) Obviousness of Claims 9, 19 and 21: Storage Stability

Claim 19 depends from claim 13, and further limits claim 13 by reciting that the stable aqueous liquid preparation 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. Claims 9 and 21 depend from claims 7 and 19, respectively, and further limit their respective base claims by reciting that the stable aqueous liquid preparation 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. Thus, claims 9, 19, and 21 each further limit their respective base claims only by reciting a property of storage stability.

Claims 7 and 13, from which claims 9, 19, and 21 directly or indirectly 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 '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. 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 9, 19, and 21 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.

n) Obviousness of Claims 10, 16 and 22: Amounts of Bromfenac and Tyloxapol

Claims 10, 16, and 22 depend from claims 7, 13, and 21, respectively, and further limit their respective base claims by reciting that:

> the first component in the composition of claim 1 is a 2-amino-3-(4-bromobenzoyl)phenylacetic acid (bromfenac) sodium salt in a concentration of from about 0.01 to about 0.2 w/v %; and
>
> the second component in the composition of claim 1 is tyloxapol in a concentration of from about 0.01 w/v % to about 0.05 w/v %.

As previously discussed, claim 7, 13, and 21 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.

The '225 patent recites 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 10, 16, and 22. *'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 10, 16, and 22. *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.[13] 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 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 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 allegedly encompassed by claims 10, 16, and 22.

Claims 10, 16, 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.

o) Obviousness of Claim 20: Quaternary Salt

Claim 20 depends from claim 19, and further limits claim 19 by reciting that the composition further comprises a quaternary ammonium salt.

As previously discussed, claim 19 is 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.

Benzalkonium chloride is defined in the specification of the '131 patent as a quaternary ammonium salt. *'131 patent*, col. 2, ll. 23-29.

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

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 claim 2. *'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. *Id.*, Formulation 3 on page 7.

The '011 patent teaches a formulation containing an ophthalmologically effective amount of an NSAID in combination with "a preservative system formed of a quaternary ammonium preservative and a nonionic polyoxyethylated octylphenol surfactant, all in an aqueous vehicle." *Id.*, Abstract.

Accordingly, the prior art teaches use of quaternary ammonium compounds in aqueous formulations of 3-benzoylphenyl acetic acid NSAIDs, including bromfenac, and nonionic polyoxyethylated octylphenol surfactants. Therefore, claim 20 is 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.

p) Obviousness of Claim 23: pH of About 7.5 to About 8.5

Claim 23 depends from claim 22, respectively, and further limits claim 22 by reciting that the pH of the aqueous liquid preparation is from about 7.5 to about 8.5.

As discussed above, claim 22 is 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.

The formulation of Example 6 of the '225 patent has a pH of 8, as encompassed by claim 23. *'225 patent*, Example 5.

The formulation of Formulation 3 of the '804 publication has a pH of 7.5, as encompassed by claim 23. *'804 publication*, Formulation 3.

Accordingly, a person of ordinary skill would have found it obvious to prepare the formulation of claim 22 at a pH of between 7.5 and 8.

Therefore, claim 23 is 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.

q) Obviousness of Claims 25, 26, 27, 28 and 29: Preservative Efficacy Standard

Claims 25, 26, 27, 28, and 29 depend from claims 1, 4, 7, 9, and 13, respectively, and further limit their base claims by reciting that the claimed 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.

Thus, claims 25, 26, 27, 28, and 29 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, 4, 7, 9, and 13, from which claims 25, 26, 27, 28, and 29 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.

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 25, 26, 27, 28, and 29 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.

r) Obviousness of Claim 20: Additive

Claim 30 depends from claim 1, and further limits claim 1 by reciting that the formulation further comprises one or more additives selected from the group consisting of a preservative, buffer, thickener, stabilizer, chelating agent, and pH controlling agent.

As discussed above, claim 1 is 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 '804 publication describes a topical formulation comprising a derivative of 3-benzoylphenylacetic acid, as the sole active ingredient; polysorbate 80 (0.01 w/v%); 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 (0.01 w/v%); and benzalkonium chloride. *'804 publication*, Formulation 3 on page 7.

The '804 publication further teaches that the disclosed formulations "can be topically administered to the eye," and that they may include excipients. *'804 publication*, p. 5, ll. 20-32.

> Aqueous eye drops, gels and ointments can be formulated according to conventional technology and would include one or more excipients. For example, topically administrable compositions may contain tonicity-adjusting agents, such as mannitol or sodium chloride; *preservatives* such as chlorobutanol, benzalkonium chloride, polyquaternium-1, or chlorhexidine; *buffering agents*, such as phosphates, borates, carbonates and citrates; and *thickening agents*, such as high molecular weight carboxy vinyl polymers, including those known as carbomers, hydroxyethylcellulose, or polyvinyl alcohol.

Id. (emphasis added).

Accordingly, it would have been obvious to a person of ordinary skill in the art to modify the formulation of Example 6 of the '225 patent by adding a preservative, a buffer, or a thickener, as suggested by the '804 publication. Claim 30 is 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.

D. NON-INFRINGEMENT OF THE '131 PATENT

As set forth in detail above, each of claims of the '131 patent is invalid under 35 U.S.C. § 103. Because the claims of the '131 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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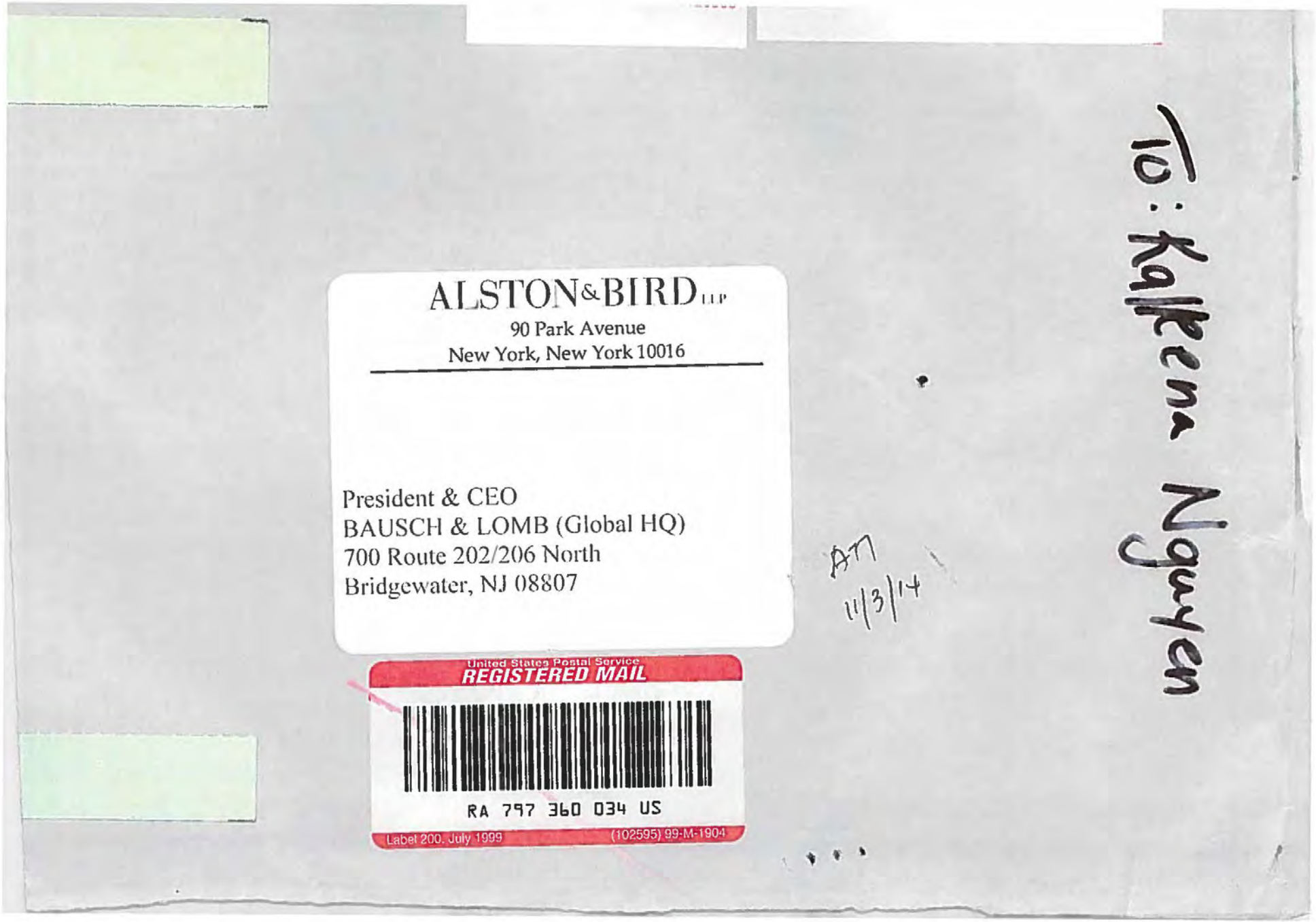
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