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September 19, 2014

CONFIDENTIAL

VIA FEDEX OVERNIGHT DELIVERY[1]

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President & CEO
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Re: ANDA No. 206326 (Bromfenac) Notification of Certification of Noninfringement and/or Invalidity for U.S. Patent Nos. 8,129,431 and 8,669,290 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 it has filed an 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 each of U.S. Patent Nos. 8,129,431 ("the '431 patent") and 8,669,290

[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 and address for the '431 patent are taken from the USPTO's web-based assignment records accessed on September 19, 2014. Assignment data for the '290 patent is not currently available on the USPTO's web-based assignment records.

[redacted]

("the '290 patent") is invalid, unenforceable, and/or will not be infringed by the manufacture, use, sale, offer for sale, or importation of Innopharma's Bromfenac Product as defined by Innopharma's ANDA No. 206326.

Innopharma's ANDA is for a 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 submitted its ANDA under 21 U.S.C. § 355(j)(1) and (2)(A) with Paragraph IV certifications to the '431 and the '290 patents (collectively "the Orange Book Patents"), which are 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. According to the FDA's Orange Book:

- the '431 patent will expire on September 11, 2025; and
- the '290 patent will expire on January 16, 2024.

Innopharma alleges, and has certified to the FDA that, to the best of Innopharma's knowledge, each of the Orange Book Patents 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.

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 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:

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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,

Thomas J. Parker

Enclosures: Exhibits A & B

EXHIBIT A

Table of Contents

[redacted]

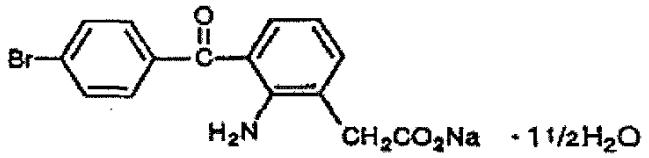
EXHIBIT A
DETAILED STATEMENT OF THE FACTUAL AND LEGAL BASIS FOR INNOPHARMA LICENSING INC.'S CERTIFICATION THAT U.S. PATENT NOS. 8,128,431 AND 8,669,290 ARE INVALID, UNENFORCEABLE, AND/OR WILL NOT BE INFRINGED BY THE MANUFACTURE, USE, SALE, OFFER FOR SALE, OR IMPORTATION OF INNOPHARMA'S BROMFENAC PRODUCT AS DEFINED BY ANDA NO. 206-326

For at least the reasons set forth below, U.S. Patent Nos. 8,128,431 ("the '431 patent") and 8,669,290 ("the '290 patent") do not prohibit Innopharma Licensing Inc ("Innopharma") from manufacturing, using, selling, offering for sale, or importing Innopharmas'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 '431 patent; and 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.

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 Orange Book Patents for at least the following reasons:

The '431 Patent

As set forth in detail below, Innopharma cannot infringe claims 1-22 of the '431 patent because each of these claims is invalid under 35 U.S.C. § 103 as follows:

- Independent Claim 1 of the '431 patent would have been obvious under 35 U.S.C. § 103 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 No. 5,414,011 ("the '011 patent"), and Regev and Zana, *Journal of Colloid and Interface Science* (210) 8-17 (1999) ("Regev").

- Independent Claim 1 of the '431 patent would have been obvious under 35 U.S.C. § 103 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, and U.S. Patent No. 2,454,541 ("the '541 patent").

- Independent Claim 1 of the '431 patent would have been obvious under 35 U.S.C. § 103 in light of the '225 patent in view of U.S. Patent No. 6,107,343 ("the'343 patent") and U.S. Patent No. 6,274,609 ("the '609 patent"); or alternatively, in light of the '343 patent in view of the '225 patent and Hara, Yoshiyuki, *Clinics & Drug Therapy*, 2002, 19:1014-1015 ("Hara").

- Dependent Claims 2-17 of the '431 patent would have been obvious under 35 U.S.C. § 103, in light of (A) the '225 Patent in view of the '804 Publication, the '011 Patent, and Regev; or alternatively, (B) the '225 Patent in view of the '804 publication, the '011 patent, Yuan, and the '541 patent; or alternatively, (C) the '225 patent in view the '343 patent and the '609 patent; or alternatively, (D) the '343 patent in view of the '225 patent and Hara.

- Independent Claim 18 of the '431 patent would have been obvious under 35 U.S.C. § 103 in light of the '225 patent in view of the '804 Publication, the '011 Patent, and Regev; or, alternatively, in view of the '804 publication, the '011 patent, Yuan, and the '541 patent.

- Dependent Claims 19-22 of the '431 patent would have been obvious under 35 U.S.C. § 103 in light of (A) the '225 patent in view of the '804 Publication, the '011 Patent, and Regev; or alternatively, (B) the '225 patent in view of the '804 publication, the '011 patent, Yuan, and the '541 patent; or alternatively, (C) the '225 patent in view the '343 patent and the '609 patent; or alternatively, (D) the '343 patent in view of the '225 patent and Hara.

The '290 Patent

As set forth in detail below, Innopharma cannot infringe claims 1-22 of the '290 patent because each of these claims is invalid under 35 U.S.C. § 103 as follows:

- Independent Claims 1 and 14 of the '290 patent would have been obvious under 35 U.S.C. § 103 in light of the '225 patent in view of the '804 publication, the '011 patent, and Regev.
- Independent Claims 1 and 14 of the '290 patent would have been obvious under 35 U.S.C. § 103 in light of the '225 patent in view of the '804 publication, the '011 patent, Yuan, and the '541 patent.
- Independent Claims 1 and 14 of the '290 patent would have been obvious under 35 U.S.C. § 103 over the '225 patent in view of the'343 patent and the '609 patent; or alternatively, over the '343 patent in view of the '225 patent and Hara.
- Independent Claim 8 of the '290 patent would have been obvious under 35 U.S.C. § 103 in light of the '225 patent in view of the '804 Publication, the '011 Patent, and Regev; or, alternatively, in view of the '804 publication, the '011 patent, Yuan, and the '541 patent.
- Independent Claim 8 of the '290 patent would have been obvious under 35 U.S.C. § 103 in light of the '225 patent in view of the'343 patent and the '609 patent, or alternatively; over the '343 patent in view of the '225 patent and Hara.
- Dependent Claims 2-7 and 9-30 of the '290 patent would have been obvious under 35 U.S.C. § 103 in light of (A) the '225 patent in view of the '804 Publication, the '011 Patent, and Regev; or alternatively, (B) the '225 patent in view of the '804 publication, the '011 patent, Yuan, and the '541 patent; or alternatively, (C) the '225 patent in view the '343 patent and the '609 patent, or alternatively, (D) the '343 patent in view of the '225 patent and Hara.

III. Analysis

A. General Legal Principles

1. Burdens and Presumptions

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

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

2. Claim Construction

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

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

Where the specification contains nothing to indicate that phrases are to be given anything other than their ordinary meanings, then those are the meanings the court must give them. *See, e.g., Vitronics*, 90 F.3d at 1582. Thus, a technical term used in a patent document is interpreted as having the meaning that it would be given by persons experienced in the field of the patent, unless it is apparent from the specification or the prosecution history that the patentee used the term with a different meaning. *See, e.g., CVI/Beta Ventures, Inc. v. Tura Lp*, 112 F.3d 1146, 1153 (Fed. Cir. 1997) (citation omitted) ("[i]t is always necessary to review the specification to

determine whether the inventor has used any terms in a manner inconsistent with their ordinary meaning."). In addition, unambiguous claim language controls over alternative contradictory interpretations found in the specification. *See, e.g., Elekta Instrument S.A. v. UR Scientific Intl, Inc.*, 214 F.3d 1302, 1308 (Fed. Cir. 2000).

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

3. Invalidity Analysis

Once the claims have been properly construed, in the case of an invalidity analysis, the second step requires the properly construed claims to be compared to the prior art reference(s) to determine whether the claim limitations are present in the prior art, either expressly or inherently. *See, e.g., Iron Grip Barbell Co., Inc. v. USA Sports, Inc.*, 392 F.3d 1317, 1323 (Fed. Cir. 2004); *In re Schreiber*, 128 F.3d 1473, 1477 (Fed. Cir. 1997). Whether a limitation is present in a prior art reference is a factual determination and thus may be submitted to a jury if the case is not tried to the court. *See Rapoport*, 254 F.3d at 1060. However, whether a claim is obvious in view of the prior art is a question of law that is subject to underlying factual determinations. *Id.* at 1057-58. The disclosure of the specification must also be examined with respect to each construed claim to determine if it meets the legal standards for written description. *University of Rochester v. G.D. Searle & Co., Inc.*, 358 F.3d 916, 921 (Fed. Cir. 2004).

4. Obviousness Under 35 U.S.C. § 103

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

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

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

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

(d) evaluating evidence of secondary considerations.

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

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

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

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

In the *KSR* case, the Supreme Court rejected the Federal Circuit's rigid rule of requiring that there be an explicit teaching, suggestion, or motivation to combine references to make the claimed invention. 550 U.S. at 415. Instead, the Court found that other factors, including the availability of design or market pressures, may provide the motivation to make the claimed invention. "When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue" known options available to make the claimed invention. *Id.* at 421. The Court in *KSR* also held that if a combination or improvement is no more than a predictable use of prior art elements, that combination would have been obvious to one of ordinary skill in the art. *Id.* at 416. The Court recognized the creativity of an ordinary practitioner, and that a skilled artisan may "be able to fit the teachings of multiple patents together like pieces of a puzzle." *Id.* at 420. "A person of ordinary skill is also a person of ordinary creativity, not an automaton." *Id.* at 421.

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

a) Level of Ordinary Skill in the Art

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

b) Scope and Content of the Prior Art

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

Furthermore, in determining obviousness, both prior art references and general knowledge in the art can be considered. *See, e.g., Leapfrog Enterprise Inc. v. Fisher-Price Inc.*, 485 F.3d 1157, 1161 (Fed. Cir. 2007) ("We agree with Fisher-Price that the district court correctly concluded that the subject matter of claim 25 of the '861 patent would have been obvious in view of the combination of Bevan, the SSR, and the knowledge of one of ordinary skill in the art. An obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not.") *See KSR*, 550 U.S. at 420-21.

c) Differences between the Prior Art and the Claimed Invention

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

matter to the prior art were "exceedingly small and quite nontechnical" and that the device was "old in the art." *Graham*, 383 U.S. at 36-37. Accordingly, the degree of differences between the prior art and the claimed invention may be useful to a reviewing court in determining whether an invention is obvious.

1. 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 Textifarben GmbH v. C.H. Patrick, Co.*, 464 F.3d 1356, 1361 (Fed. Cir. 2006)).[2]

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,

[2] 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).[3]

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 argued 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

[3] 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.[4] 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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[4] "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 argued 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).

2. 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. THE LISTED ORANGE BOOK PATENTS FOR PROLENSA™

The Orange Book lists two patents for PROLENSA™:

1. U.S. Patent No. 8,128,431

a) Priority Information and Related Applications

U.S. Patent No. 8,129,431 ("the '431 Patent") (Exhibit 2) issued March 6, 2012 from U.S. Application Serial No. 10/525,006 ("the '006 Application") as a U.S. National Stage Application based on International Application PCT/JP2004/000350, filed on January 16, 2004, which claims priority to Japanese Application No. JP 2003-12427, filed January 21, 2003.

The '431 Patent contains twenty-two claims. The named inventors are Shirou Sawa and Shuei Fujita, both of whom assigned the '431 Patent to the Senju Pharmaceutical Co., Ltd. on

March 14, 2005. The assignment was recorded at the USPTO on March 28, 2005. The '431 Patent is listed to expire on September 11, 2025.[5]

b) Claims of the '431 Patent

The twenty-two claims of the '431 Patent are listed below:

1. An aqueous liquid preparation consisting essentially of the following two components, wherein the first component is 2-amino-3-(4-bromobenzoyl)phenylaceticacid 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 the second component is tyloxapol, 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 benzalkonium chloride.

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

3. The aqueous liquid preparation according to claim 1, wherein the second component is tyloxapol and the pharmacologically acceptable salt of 2-amino-3-(4-bromobenzoyl)phenylacetic acid is a sodium salt , wherein the concentration of the tyloxapol is from about 0.01 w/v % to about 0.5 w/v %; and wherein the first component is a 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.01 to about 0.5 w/v %.

4. The aqueous liquid preparation according to claim 3, wherein the concentration of the tyloxapol is from about 0.01 w/v % to about 0.3 w/v % and the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.05 to about 0.2 w/v %.

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

6. The aqueous liquid preparation according to claim 4, wherein the concentration of the tyloxapol is about 0.02 w/v %.

7. The aqueous liquid preparation according to claim 1, wherein the formulation further includes one or more additives selected from the group consisting of a preservative, buffer, thickener, stabilizer, chelating agent, and pH controlling agent.

[5] The cited expiration date of the '431 Patent is based upon information available in the FDA Orange Book. *See* FDA Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations at http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm.

8. The aqueous liquid preparation according to claim 7, wherein said preservative is benzalkonium chloride; wherein said buffer is boric acid and/or sodium borate; wherein said thickener is polyvinylpyrrolidone; wherein said stabilizer is sodium sulfite; wherein said chelating agent is sodium edetate; and wherein said pH controlling agent is sodium hydroxide.

9. The aqueous liquid preparation according to claim 8, wherein the pH is from about 7 to about 9.

10. The aqueous liquid preparation according to claim 8, wherein the pH is from about 7.5 to about 8.5.

11. The aqueous liquid preparation according to claim 4, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is about 0.2 w/v %.

12. The aqueous liquid preparation according to claim 4, wherein the concentration of the tyloxapol is about 0.3 w/v %.

13. The aqueous liquid preparation according to claim 12, wherein the formulation further includes one or more additives selected from the group consisting of a preservative, buffer, thickener, stabilizer, chelating agent, and pH controlling agent.

14. The aqueous liquid preparation according to claim 13, wherein said preservative is benzalkonium chloride; wherein said buffer is boric acid and/or sodium borate; wherein said thickener is polyvinylpyrrolidone; wherein said stabilizer is sodium sulfite; wherein said chelating agent is sodium edetate; and wherein said pH controlling agent is sodium hydroxide.

15. The aqueous liquid preparation according to claim 11, wherein the concentration of the tyloxapol is about 0.02 w/v %.

16. The aqueous liquid preparation according to claim 15, wherein the formulation further includes one or more additives selected from the group consisting of a preservative, buffer, thickener, stabilizer, chelating agent, and pH controlling agent.

17. The aqueous liquid preparation according to claim 16, wherein said preservative is benzalkonium chloride; wherein said buffer is boric acid and/or sodium borate; wherein said thickener is polyvinylpyrrolidone; wherein said chelating agent is sodium edetate; and wherein said pH controlling agent is sodium hydroxide.

18. 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, 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.

19. The aqueous liquid preparation of claim 18, wherein (a) is a 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt.

20. The aqueous liquid preparation of claim 19, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.01 to about 0.5 w/v % and the concentration of the tyloxapol is about 0.02 w/v %.

21. The aqueous liquid preparation of claim 20, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is about 0.01 w/v %.

22. The aqueous liquid preparation of claim 20, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is about 0.1 w/v %.

c) Specification of the '431 Patent

According to the'431 Patent, the purported "invention relates to 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." *'431 patent, col. 1, ll. 11-20.* The specification further alleges 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. 14-22.*

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. 4-10.*

The specification alleges that the stability of sodium 2-amino-3-(4-bromobenzoyl)phenylacetate in an eye drop formulation is greatest in a tyloxapol-containing preparation and poorest in a polysorbate 80-containing preparation. *Id., col. 7, ll. 10-64.* According to the specification, 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 purportedly 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.*

d) Prosecution History of the '431 Patent

The prosecution history of the '431 patent is attached as Exhibit 3. The application that led to the '431 Patent was filed as U.S. Appl. Serial No. 10/525,006 ("the '006 Application") on March 28, 2005 as a U.S. National Stage Application based on International Application PCT/JP2004/000350, filed on January 16, 2004, which claims priority to Japanese Application No. JP 2003-12427, filed January 21, 2003.

i) The '006 Application Claims as Filed

The '006 Application entered U.S. national stage on February 17, 2005 with original claims 1-18:

1. 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.

2. The aqueous liquid preparation according to claim 1, wherein the alkyl aryl polyether alcohol type polymer has a polymerization degree of 3 to 10, the alkyl contains 1 to 18 carbon atoms, the aryl is a phenyl residue, and the polyether alcohol is represented by the formula $0(CH_2CH_2O)_XH$ in which X is an integer of 5 to 100.

3. The aqueous liquid preparation according to claim 1 or 2, wherein the alkyl aryl polyether alcohol type polymer is tyloxapol.

4. The aqueous liquid preparation according to claim 1, wherein the carbon number of the fatty acid in the polyethylene glycol fatty acid ester is 12 to 18.

5. The aqueous liquid preparation according to claim 1 or 4, wherein the polyethylene glycol fatty acid ester is polyethylene glycol monostearate.

6. The aqueous liquid preparation according to any one of claims 1 to 3, wherein the concentration of the alkyl aryl polyether alcohol type polymer is selected from a range of minimum concentration of 0.01 w/v % to maximum concentration of 0.5 w/v %.

7. The aqueous liquid preparation according to any one of claims 1, 2 or 4, wherein the concentration of the polyethylene glycol fatty acid ester is selected from a range of minimum concentration of 0.02 w/v % to maximum concentration of 0.1 w/v %.

8. The aqueous liquid preparation according to any one of claims 1 to 7, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof is 0.01 to 0. 5 w/v %.

9. The aqueous liquid preparation according to any one of claims 1 to 8, wherein benzalkonium chloride is contained as a preservative.

10. The aqueous liquid preparation according to any one of 1 to 9, wherein the pharmacologically acceptable salt of 2-amino-3-(4-bromobenzoyl)phenylacetic acid is a sodium salt.

11. The aqueous liquid preparation according to any one of claims 1 to 10, wherein the pH of the aqueous liquid preparation is within a range of 7 to 9.

12. The aqueous liquid preparation according to claim 11, wherein the pH of the aqueous liquid preparation is within a range of 7.5 to 8.5.

13. The aqueous liquid preparation according to any one of claims 1 to 12, wherein the aqueous liquid preparation is an eye drop.

14. The aqueous liquid preparation according to any one of claims 1 to 12, wherein the aqueous liquid preparation is a nasal drop.

[redacted]

15. An eye drop comprising sodium 2-amino-3-(4-bromobenzoyl)phenylacetate hydrate and 0.01 to 0.5 w/v % of tyloxapol.

16. An eye drop comprising sodium 2-amino-3-(4-bromobenzoyl)phenylacetate hydrate and 0.02 to 0.1 w/v % of polyethylene glycol monostearate.

17. A method for stabilizing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof in an aqueous liquid preparation, which comprises incorporating tyloxapol or polyethylene glycol monostearate into an aqueous liquid preparation containing 2-amino-3- (4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof .

18. A method for inhibiting decrease in preservative effect of a preservative in an aqueous liquid preparation of 2 -amino- 3 - (4 - bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, which comprises incorporating tyloxapol or polyethylene glycol monostearate into an aqueous liquid preparation containing 2 -amino- 3 - (4-bromobenzoyl)phenylacetic acid or a 10 pharmacologically acceptable salt thereof or a hydrate thereof and a preservative.

ii) Preliminary Amendments Dated February 17, 2005; March 20, 2007; and April 3, 2007

On February 17, 2005, Applicants filed a Preliminary Amendment that reduced the multiple dependencies in the pending claims. In particular, claims 3, 5-11, and 13-14 were amended to depend solely from claim 1.

On March 20, 2007, Applicants filed a second Preliminary Amendment that cancelled claims 1-18 and presented new claims 19-40 as follows:

19. (New) 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.

20. (New) The aqueous liquid preparation according to claim 19, wherein the alkyl aryl polyether alcohol type polymer is tyloxapol; wherein the concentration of the tyloxapol is selected from a range of about 0.01 w/v % to about 0.5 w/v %; and wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof is selected from a range of about 0.01 to about 0.5 w/v %.

21. (New) The aqueous liquid preparation according to claim 20, wherein the pharmacologically acceptable salt of 2-amino-3-(4-bromobenzoyl)phenylacetic acid is a sodium salt.

22. (New) The aqueous liquid preparation according to claim 21, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is selected from a range of about 0.05 to about 0.2 w/v %.

23. (New) The aqueous liquid preparation according to claim 22, wherein the concentration of the tyloxapol is selected from a range of about 0.01 w/v % to about 0.3 w/v %.

24. (New) The aqueous liquid preparation according to claim 23, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is about 0.1 w/v %.

25. (New) The aqueous liquid preparation according to claim 24, wherein the concentration of the tyloxapol is about 0.02 w/v %.

26. (New) The aqueous liquid preparation according to claim 25, wherein the formulation further includes one or more additives selected from the group consisting of a preservative, buffer, thickener, stabilizer, chelating agent, and pH controlling agent.

27. (New) The aqueous liquid preparation according to claim 26, wherein said preservative is benzalkonium chloride; wherein said buffer is boric acid and/or sodium borate; wherein said thickener is polyvinylpyrrolidone; wherein said stabilizer is sodium sulfite; wherein said chelating agent is sodium edetate; and wherein said pH controlling agent is sodium hydroxide.

28. (New) The aqueous liquid preparation according to claim 27, wherein the pH is from about 7 to about 9.

29. (New) The aqueous liquid preparation according to claim 28, wherein the pH is from about 7.5 to about 8.5.

30. (New) The aqueous liquid preparation according to claim 27, wherein said liquid preparation is in the form of an eye drop.

31. (New) The aqueous liquid preparation according to claim 23, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is about 0.2 w/v %.

32. (New) The aqueous liquid preparation according to claim 31, wherein the concentration of the tyloxapol is about 0.3 w/v %.

33. (New) The aqueous liquid preparation according to claim 32, wherein the formulation further includes one or more additives selected from the group consisting of a preservative, buffer, thickener, stabilizer, chelating agent, and pH controlling agent.

34. (New) The aqueous liquid preparation according to claim 33, wherein said preservative is benzalkonium chloride; wherein said buffer is boric acid and/or sodium borate; wherein said thickener is polyvinylpyrrolidone; wherein said stabilizer is sodium sulfite; wherein said chelating agent is sodium edetate; and wherein said pH controlling agent is sodium hydroxide.

35. (New) The aqueous liquid preparation according to claim 34, wherein said liquid preparation is in the form of an eye drop.

36. (New) The aqueous liquid preparation according to claim 31, wherein the concentration of the tyloxapol is about 0.02 w/v %.

37. (New) The aqueous liquid according to claim 36, wherein the formulation further includes one or more additives selected from the group consisting of a preservative, buffer, thickener, stabilizer, chelating agent, and pH controlling agent.

38. (New) The aqueous liquid preparation according to claim 37, wherein said preservative is benzalkonium chloride; wherein said buffer is boric acid and/or sodium borate; wherein said thickener is polyvinylpyrrolidone; wherein said chelating agent is sodium edetate; and wherein said pH controlling agent is sodium hydroxide.

39. (New) A method for stabilizing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof in an aqueous liquid preparation, which comprises incorporating tyloxapol or polyethylene glycol monostearate into an aqueous liquid preparation containing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof.

40. (New) A method for inhibiting decrease in preservative effect of a preservative in an aqueous liquid preparation of 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, which comprises incorporating tyloxapol or polyethylene glycol monostearate into an aqueous liquid preparation containing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof and a preservative.

On April 3, 2007, Applicants filed a third Preliminary Amendment that amended claim 37 to recite "[t]he aqueous liquid preparation according to claim 36".

iii) Restriction Requirement Mailed on May 23, 2007

In a Restriction Requirement mailed May 23, 2007, the Examiner restricted originally filed claims 1-18 into three distinct inventions:

(I) Claims 1-16, drawn to an aqueous liquid preparation;
(II) Claim 17, drawn to a method for stabilizing 2-amino-3-(4-bromobenzoyl)phenylacetic acid;
(III) Claim 18, drawn to a method for inhibiting decrease in preservative effect of a preservative in an aqueous liquid preparation of 2-amino-3-(4-bromobenzoyl)phenylacetic acid.

The Examiner asserted that the inventions were distinct, each from the other for the following reasons:

> The inventions listed as Groups I-III do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the technical feature common to all the claims is the sodium salt/hydrate of 2-amino-3-(4-bromobenzoyl) phenylacetic

> acid (also known as bromfenac sodium hydrate) in an aqueous liquid preparation. Such a preparation has been disclosed in "New Drugs in Japan, 2001" (translation of table (2), provided by applicant). Therefore, since the technical feature common to the claims was known in the art at the time of the invention, no corresponding special technical feature is present in the claims.

Restriction Requirement, p. 2.

iv) Applicants' Response Dated June 4, 2007

On June 4, 2007, Applicants filed an Amendment that amended claim 37 to "[t]he aqueous liquid preparation according to claim 36 [...]."

In response to the Restriction Requirement, Applicants remarked that claims 1-18 were cancelled and new claims were added in a Second Preliminary Amendment April 3, 2007. Applicants also requested the Examiner issue a new restriction Requirement. *Response, p. 1.*

v) Restriction Requirement Mailed on July 24, 2007

In a Restriction Requirement mailed July 24, 2007, the Examiner acknowledged the Preliminary Amendment filed April 3, 2007 and restricted pending claims 19-40 into three distinct inventions:

(I) Claims 19-38, drawn to an aqueous liquid preparation;
(II) Claim 39, drawn to a method for stabilizing 2-amino-3-(4-bromobenzoyl)phenylacetic acid;
(III) Claim 40, drawn to a method for inhibiting decrease in preservative effect of a preservative in an aqueous liquid preparation of 2-amino-3-(4-bromobenzoyl)phenylacetic acid.

The Examiner asserted that the inventions were distinct, each from the other for the following reasons:

> The inventions listed as Groups I-III do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the technical feature common to the claims is 2-amino-3-(4-bromobenzoyl)phenylacetic acid (bromfenac) with a second component (an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester) in an aqueous liquid preparation. Desai et al. (WO 96/14829; IDS Ref. AJ) teaches aqueous ophthalmic compositions (example 1) consisting of, inter alia, bromfenac (claim 5), with optional components, including tyloxapol (an alkyl aryl polyether alcohol type polymer (p.4, line 29). Since the technical feature has previously been disclosed, there is no unifying corresponding technical feature.

Restriction Requirement, p. 2-3.

vi) Applicants' Response Dated August 20, 2007

On August 20, 2007, Applicants filed a Response to the the Restriction Requirement with an election to Group I, claims 19-38 and a species election to claim 20.

vii) Non-Final Office Action Mailed September 27, 2007

In a Non-final Office Action mailed on September 27, 2007, the Examiner stated that foreign priority to JP 2003-012427, filed January 21, 2003 was acknowledged; however because no translation was provided, the prior art was determined with reference to the priority date for the PCT application date, PCT/JP/04/00350, filed January 16, 2004. *Non-final Office Action, p. 2-3.*

Claims 19-24 and 31 were rejected under 35 U.S.C. § 102(b) as anticipated by WO 01/15677 to Gamache *et al.* ("Gamache"). The Examiner stated that:

> Gamache teaches all of the components of the claims: compositions for otic and intranasal use (p.6, lines 5-6) that contain a combination of a 5-HT agonist and an anti-inflammatory agent (p. 6, lines 1-4; p. 12 lines 9-10) or alternatively sequential or concurrent dosing of separate compositions that contain the 5-HT antagonist in one composition and the anti-inflammatory agent in a second composition (p. 12, lines 9-11); specifically claimed is the anti-inflammatory specie bromfenac (the first compound of instant claim 19; claim 11;); 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; p. 13, lines 6-8); aqueous formulations are preferred (p. 10, lines 11-14); tyloxapol is taught at the concentration of 0.05 % (w/v) (p. 16, line 30). It is noted that claim 21 and further dependent claims limit the options for the salt of bromfenac to the sodium salt, and that the specific concentrations recited in dependent claims apply to the sodium salt; the other options (bromfenac or a hydrate of bromfenac) are still viable choices that are part of the claims 21 and dependent claims (which depend on and include the options of claim 20). Gamache anticipates 1) the claim to bromfenac in the concentration range of claim 20 (which is also an option of claims 21-24 and 31). 2) The form of bromfenac in solution will be the same when the acid is dissolved in a solution followed by adjustment to the desired pH with NaOH/HCI (Gamache, p. 15, line 33) as when the sodium salt is dissolved in solution adjusted to the same pH; for this, case Gamache also anticipates the sodium salt limitation of claim 21, albeit not the sodium salt concentration limitation of claim 22 and further dependent claims, since the claim is drawn to an aqueous liquid preparation, irrespective of how it is prepared.

Non-final Office Action, p. 3-4.

The Examiner also rejected claim 19 under 35 U.S.C. § 102(b) as anticipated by U.S. Patent No. 6,319,513 to Dobrozsi ("Dobrozsi"). The Examiner stated that "Dobroszi teaches aqueous liquid compositions comprising a pharmaceutically active agent selected from a group that includes analgesics (abstract); a specie taught is bromfenac (column 10, line 11); tyloxapol is taught at 0.15 and 0.035 % (Example 10)." *Id., p. 5.*

The Examiner also rejected claims 19-38 under under 35 U.S.C. § 102(e) as anticipated by U.S. Patent Appl. No. 2007/0082857 to Sawa ("Sawa"). The Examiner stated that:

> Sawa teaches the elements of the claims: aqueous solution preparations comprising an aminoglycoside antibiotic and bromfenac or a salt of bromfenac (abstract); bromfenac sodium and bromfenac sodium hydrate is taught at 0.1 and 0.2 % (Tables 1, 3, 6, 9-15); tyloxapol at 0.3 °A) resulted in solutions that were clear, when the control (no additive) was turbid (Table 5, 8), tyloxapol is also taught at 0,02 °A) (Table 15); additives taught include benzalkonium chloride (Table 8), boric acid (Tables 9, 12), sodium edentate (Table 15), and sodium hydroxide (Table 15); pH values include 7.5, 7.8 and 8.0 (Tables 9-15); eye drop formulations are also taught (Examples 1-7). It is noted that the aqueous preparations contain an active ingredient not in the instant claims. However, Sawa still anticipates the instant claims, due to the open language construction of the claims (use of "comprising").

Id., p. 5-6.

The Examiner also rejected claims 19-29, 31-34, and 36-38 under 35 U.S.C. § 103(a) as obvious over Gamache and ISTA Pharmaceuticals news release "New Drug Applications: Xibrom," (http://www.drugs.com/nda/xibrom_040525.html) ("ISTA Pharmaceutical news release") or Nolan *et al.*, "The Topical Anti-inflammatory and Analgesic properties of Bromfenic in Rodents", *Agents and Actions*, Aug 1988, 25(1-2): 77-85 ("Nolan"). The Examiner stated that:

> Claims 19-24 and 31 are rejected as outlined above. With respect to claims 21-38 (claims 21-24 and 31, with respect to the sodium salt of bromfenic and associated concentrations), in addition to the points made above, Gamache also teaches the additives and pH of the instant claims, edetate disodium, benzylalkonium chloride, sodium hydroxide, and a pH of 7.3-7.4 (Example 2); polyvinyl pyrrolidone (p. 14, line 5); and sodium borate buffer (p. 13, line 11). Gamache does not specifically teach the sodium salt of bromfenic, nor a hydrate, nor the concentration range or specific bromfenic sodium concentrations of 0.05-0.2, or at 0.1 or 0.2 %, nor the tyloxapol concentrations of 0.02 or 0.3 %. The ISTA Pharmaceuticals news release demonstrates that products containing 0.1 % bromfenac sodium acquired US marketing rights for Xibrom in May 2002 (were known by others in this country

> before applicant's priority date, a 35 USC 102(a) date). Nolan teaches bromfenac (the sodium salt, sesquihydrate form) was effective as a topical analgesic at concentrations of 0.1-0.32 % in mice and more potent than the other drugs tested (abstract). 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, sesquihydrate of 0.1, about 0.2 and about 0.32 %, in the invention of Gamache, since these values have demonstrated efficacy for topical use. It would have been obvious to adjust the concentration of tyloxapol, to see what the effect would be on the solubility and stability of the aqueous preparations, which would have resulted in the effective concentrations of the instant claims. 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, bromfenic, in a more aqueous soluble ionic form. The motivation would have been to prepare pharmaceutical products with optimal drug dosage and stability.

Id., p. 7-8.

The Examiner also rejected claims 19-30 under 35 U.S.C. § 103(a) as obvious over Yakuji Nippo Ltd. "New Drugs in Japan" 2001 ("Yakuji Nippo") and U.S. Patent No. 6,369,112 to Xia. The Examiner stated that:

> Yakuji Nippo teaches a bromfenac sodium sesquihydrate ophthalmic formulation that contains: 0.1% (w/v) bromfenac (items 1-3); boric acid buffer, sodium sulfite, disodium eentate, polyvinylpyrrolidone, and benzalkonium chloride (item 2, additives); a pH of 8.0-8.6 (item 2, pH). Yakuji Nippo does not teach tyloxapol. Xia teaches a solution useful for contact lenses that provides enhanced cleaning and disinfecting efficacy of the contact lens (abstract), which contains tyloxapol as one of three ingredients (abstract; column 3, lines 7-21); tyloxapol is taught at concentrations of 0.25 and 0.025 (about 0.02 and 0.3; Table 1). Xia teaches the addition of tyloxapol to the solution improves the stability and therefore the disinfecting efficacy over time of the active component (column 7, lines 8-18). It would have been obvious to one of ordinary skill in the art at the time of the invention to add tyloxapol to the ophthalmic formulation of Yakuji Nippo. The motivation to do so is that taught by Xia, the stability enhancing effect of this component on the active ingredient. There would have been an expectation of success, since tyloxapol has demonstrated efficacy with the contact lens cleaning solutions.

Id., p. 8-9.

The Examiner also rejected claims 19-38 under 35 U.S.C. § 103(a) as obvious over Yakuji Nippo and Nolan. The Examiner stated that:

> Neither Yakuji Nippo or Xia teach the bromfenac sodium hydrate solutions at a bromfenac concentration of 0.2 %. Nolan teaches topical solutions are efficacious in the concentration range of 0.1-0.32 %. It would have been obvious to one of ordinary skill in the art at the time of the invention to use a concentration of about 0.2% bromfenic sodium hydrate (right in the middle of the range Nolan teaches is effective), in the modified Yakuji Nippo ophthalmic solution with tyloxapol added. The motivation to use a higher bromfenac concentration would be to provide an option of a more concentrated solution for patients in cases where a physician determines that higher anti-inflammatory concentration is desirable, such as when the lower dosage does not completely relieve the inflammation or pain.

Id., p. 9.

The Examiner provisionally rejected claims 19-38 under nonstatutory obviousness-type double patenting as being unpatentable over claims 1-43 of copending Appl. No. 11/755,662. The Examiner stated that:

> Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application contains claims drawn to method of treating pain and/or inflammation associated with an ocular condition, by administering the aqueous solutions of the instant claims. It would have been obvious.to one of ordinary skill in the art at the time of the invention to use the formulations of the instant claims in the methods of the copending application, since the claims recite that the formulations are eye drops, and the instant abstract also teaches some of the conditions treated of the copending application.

Id., p. 10.

viii) Interview Summary Mailed March 20, 2008

In an Interview Summary mailed on March 20, 2008, the Examiner stated that an Interview with Applicants took place March 13, 2008 and that "the objection to the oath and rejections under 35 USC 102 and 103 were discussed with possible claim amendments that might be adopted." *Interview Summary.*

ix) Applicants' Response Dated March 26, 2008

On March 26, 2008, Applicants filed an Amendment that amended claims 19, 39 (withdrawn), and 40 (withdrawn), and added new claims 41-63:

> 19. (Currently Amended) An aqueous liquid preparation comprising at least 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.

39. (Withdrawn – Currently Amended) A method for stabilizing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof in an aqueous liquid preparation, which comprises incorporating tyloxapol or polyethylene glycol monostearate into an aqueous liquid preparation containing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, to obtain an aqueous liquid preparation comprising at least 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 tyloxapol or pelyethylene glycol monostearate.

40. (Withdrawn – Currently Amended) A method for inhibiting decrease in preservative effect of a preservative in an aqueous liquid preparation of 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, which comprises incorporating tyloxapol or polyethylene glycol monostearate into an aqueous liquid preparation containing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof and a preservative, to obtain an aqueous liquid preparation comprising at least 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 tyloxapol or pelyethylene glycol monostearate.

41. (New) An aqueous liquid preparation consisting essentially of at least 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.

42. (New) The aqueous liquid preparation according to claim 41, wherein the alkyl aryl polyether alcohol type polymer is tyloxapol; wherein the concentration of the tyloxapol is selected from a range of about 0.01 w/v % to about 0.5 w/v %; and wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof is selected from a range of about 0.01 to about 0.5 w/v %.

43. (New) The aqueous liquid preparation according to claim 42, wherein the pharmacologically acceptable salt of 2-amino-3-(4-bromobenzoyl)phenylacetic acid is a sodium salt.

44. (New) The aqueous liquid preparation according to claim 43, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is selected from a range of about 0.05 to about 0.2 w/v %.

45. (New) The aqueous liquid preparation according to claim 44, wherein the concentration of the tyloxapol is selected from a range of about 0.01 w/v % to about 0.3 w/v %.

46. (New) The aqueous liquid preparation according to claim 45, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is about 0.1 w/v %.

47. (New) The aqueous liquid preparation according to claim 46, wherein the concentration of the tyloxapol is about 0.02 w/v %.

48. (New) The aqueous liquid preparation according to claim 47, wherein the formulation further includes one or more additives selected from the group consisting of a preservative, buffer, thickener, stabilizer, chelating agent, and pH controlling agent.

49. (New) The aqueous liquid preparation according to claim 48, wherein said preservative is benzalkonium chloride; wherein said buffer is boric acid and/or sodium borate; wherein said thickener is polyvinylpyrrolidone; wherein said stabilizer is sodium sulfite; wherein said chelating agent is sodium edetate; and wherein said pH controlling agent is sodium hydroxide.

50. (New) The aqueous liquid preparation according to claim 49, wherein the pH is from about 7 to about 9.

51. (New) The aqueous liquid preparation according to claim 50, wherein the pH is from about 7.5 to about 8.5.

52. (New) The aqueous liquid preparation according to claim 49, wherein said liquid preparation is in the form of an eye drop.

53. (New) The aqueous liquid preparation according to claim 45, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is about 0.2 w/v %.

54. (New) The aqueous liquid preparation according to claim 53, wherein the concentration of the tyloxapol is about 0.3 w/v %.

55. (New) The aqueous liquid preparation according to claim 54, wherein the formulation further includes one or more additives selected from the group consisting of a preservative, buffer, thickener, stabilizer, chelating agent, and pH controlling agent.

56. (New) The aqueous liquid preparation according to claim 55, wherein said preservative is benzalkonium chloride; wherein said buffer is boric acid and/or sodium borate;

wherein said thickener is polyvinylpyrrolidone; wherein said stabilizer is sodium sulfite; wherein said chelating agent is sodium edetate; and wherein said pH controlling agent is sodium hydroxide.

57. (New) The aqueous liquid preparation according to claim 56, wherein said liquid preparation is in the form of an eye drop.

58. (New) The aqueous liquid preparation according to claim 53, wherein the concentration of the tyloxapol is about 0.02 w/v %.

59. (New) The aqueous liquid preparation according to claim 58, wherein the formulation further includes one or more additives selected from the group consisting of a preservative, buffer, thickener, stabilizer, chelating agent, and pH controlling agent.

60. (New) The aqueous liquid preparation according to claim 59, wherein said preservative is benzalkonium chloride; wherein said buffer is boric acid and/or sodium borate; wherein said thickener is polyvinylpyrrolidone; wherein said chelating agent is sodium edetate; and wherein said pH controlling agent is sodium hydroxide.

61. (New) A method for stabilizing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof in an aqueous liquid preparation, which comprises incorporating tyloxapol or polyethylene glycol monostearate into an aqueous liquid preparation containing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, to obtain an aqueous liquid preparation consisting essentially of at least 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 tyloxapol or polyethylene glycol monostearate.

62. (New) A method for inhibiting decrease in preservative effect of a preservative in an aqueous liquid preparation of 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, which comprises incorporating tyloxapol or polyethylene glycol monostearate into an aqueous liquid preparation containing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof and a preservative, to obtain an aqueous liquid preparation consisting essentially of at least 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 tyloxapol or polyethylene glycol monostearate, together with a preservative.

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.

With respect to the March 13, 2008 Interview, Applicants remarked that "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." *Response, p. 11.*

[redacted]

With respect to the 35 U.S.C. § 102(b) rejection of claims 19-24 and 31 as anticipated by WO 01/15677 to Gamache *et al.*, Applicants traversed and asserted that:

> The 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.
>
> On the other hand, Gamache et al. do not disclose this specific combination. Moreover the cited reference is directed to compositions comprising of 5-HT_{1D} and/or HT_{1B} agonists. The cited reference states that these agonists may be combined with an extensive list of other pharmaceutical agents, i.e. (1) anti-microbial agent, (2) anti-inflammatory agents or (3) anti-allergy agent (please see page 6, lines 1-3 of Gamache).
>
> In addition, Gamache et al. only describes "bromfenac" as one of many examples of anti-inflammatory agents enumerated on page 12, lines 11-24. Gamache et al. does not concretely describe nor suggest the claimed preparation containing bromfenac.
>
> Further, although tyloxapol (0.05% w/v) is added to an 1B/1D agonist (0.1-1.0% w/v) and moxifloxacin (0.3% w/v) in Example 4 (an Example of an otic/nasal suspension), there is no explanation about tyloxapol in the description of Gamache et al. or why it is included. Moreover in this Example, moxifloxacin is incorporated as a well-known antibacterial agent but 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 1B/1D 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.
>
> Besides, Gamache et al. is silent about an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester component according to the preparation of the present invention.
>
> Thus, Gamache et al. neither describe or suggest the specific claimed preparation of the present invention.
>
> As discussed during the interview, it is respectfully submitted that the disclosure of Gamache et al. does not constitute an "anticipation" of the claimed invention under 35 U.S.C. 102. It is not possible to

envision the specific claimed combination from the great number of possible combinations suggested by the cited reference.

Id., p. 11-12 (emphasis in original).

With respect to the 35 U.S.C. § 102(b) rejection of claim 19 as anticipated by Dobrozsi, Applicants traversed for the same reasons with respect to the rejection over Gamache *et al.*:

> Dobrozsi discloses compositions comprising colloidal particles selected from the group consisting of silica, titanium dioxide, clay, and mixtures thereof To the colloidal particle compositions may be added a great number of additional ingredients such as (1) analgesics, (2) decongestants, (3) expectorants, (4) antitussives, (5) antihistamines, (6) broncholilator, (7) topical anesthetics, (8) sensory agents, (9) oral care agents, (10) miscellaneous respiratory agents, (11) gastrointestinal agents, and mixtures thereof (please see column 2, lines 33-45 of Dobrozsi).
>
> Dobrozsi describes on column 9, line 66 - column 10, line 11 that "[t]he analgesics useful for this invention include any narcotic and non-narcotic analgesics, such as --- bromfenac, ---". That is, Dobrozsi only describes "bromfenac" as one of so many examples of agents enumerated.
>
> Further, Dobrozsi does not describe nor suggest an alkyl aryl polyether alcohol type polymer or apolvethylene glycol fatty acid ester component according to the preparation of the present invention.
>
> Besides, Dobrozsi neither describes nor suggests 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 of the claimed invention.
>
> Although tyloxapol is added to oxymethazoline hydrochloride in the preparation of mucoretentive intrasal spray decongestant (Example 10) on column 23, line 46 in Dobrozsi, no explanation about tyloxapol is given.
>
> Besides, oxymethazoline hydrochloride is a well known adrenergic, and is not an anti- inflammatory agent like bromfenac.

Id., p. 13-14 (emphasis in original).

With respect to the 35 U.S.C. § 102(e) rejection of claims 19-38 as anticipated by U.S. Patent Appl. No. 2007/0082857 to Sawa, Applicants traversed by stating that Sawa was not available as a prior art reference:

[redacted]

> The cited reference is a published U.S. patent application of a U.S. national stage application based upon PCT/JP04/16849 filed November 12, 2004. International Application No. PCT/JP2004/016849 was published in Japanese language under Publication No. W02005/046700. Please see Appendix A. Accordingly, the published patent application has no 102(e) date, nor does the published international application W02005/046700 have a 102(e) date. Please see Appendix B, which is a copy of Example 5 of the Examination Guidelines for 35 U.S.C. 102(e) published by the USPTO.
>
> Accordingly, the earliest effective date of the cited reference as a prior art reference is its publication date of April 12, 2007. Moreover, the earliest effective date of the published international application W02005/046700 is its publication date of May 26, 2005.
>
> In conclusion, the cited reference is not available as prior art against the present invention, and this ground of rejection should be withdrawn.

Id., p. 14.

With respect to the 35 U.S.C. § 103(a) rejection of claims 19-29, 31-34, and 36-38 as obvious over Gamache *et al.* and ISTA Pharmaceuticals or Nolan, Applicants asserted that:

> Gamache et al. is discussed above. This reference does not suggest the claimed invention. Gamache et al. is directed to 5-HT agonist compositions with a great number of other possible ingredients. The reference does not suggest the claimed aqueous liquid preparation comprises at least the following two components according to claims 19-38, 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.
>
> Regarding claims 41-60, the 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.
>
> The Examiners indicated during the interview that this amendment would be helpful to overcome this ground of rejection.

The cited ISTA publication was discussed during the interview. Although the cited reference has a publication date of May 25, 2004 after the effective U.S. filing date of the instant application, the reference is cited for its statement that "ISTA acquired U.S. marketing rights for Xibrom in May 2002 under a license from Senju." Thus the rejection is based upon the position that the claimed invention was known by others in the U.S. prior to the effective filing date of the instant application in the U.S. of January 16, 2004. And since the knowledgeable person(s) of ISTA is not an inventor of the invention, the reference is available as a reference under 35 U.S.C. 102(a), i.e. there is no one year grace period under 35 U.S.C. 102(b).

It should be noted that the cited reference does not disclose the claimed preparation. It does disclose a "bromfenac sodium ophthalmic solution", but it does not disclose the second claimed component comprising an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester. Nevertheless, it is understood that the PTO position is that the reference is being cited for the proposition that the claimed preparation was known in the U.S. by ISTA before the effective filing date of the instant application.

Upon inquiry, it has been determined that Xibrom has a different composition from the claimed preparation. Enclosed is a copy of the Product Insert and Material Safety Data Sheet as Appendix C. An examination of these documents show that Xibrom contains no alkyl aryl polyether alcohol type polymer or polyethylene glycol fatty acid ester, which is the second component of the claimed preparation.

There is also enclosed a ISTA Press Release about Xibrom, which states that "Xibrom, under a different trade name but identical formulation, was launched in Japan in 2000 by Senju Pharmaceuticals Co. Ltd. ISTA acquired U.S. marketing rights for Xibrom in 2002 and launched the product in the U.S. in 2005." Please see the attached Appendix D.

In summary, the cited ISTA reference fails to suggest that the claimed preparation was known in the U.S. prior to the effective filing date of the instant application. Moreover the cited ISTA reference in combination with Gamache et al. does not suggest the claimed invention.

Regarding the alternative secondary reference Nolan, only the abstract of Nolan was cited in the rejection and included with the Office Action. The abstract only teaches that bromfenac is a potent anti-inflammatory agent. It does not disclose the claimed second component. Therefore the combination of Nolan (abstract) with

> Gamache et al. does not suggest the claimed preparation comprising the at least two components.
>
> Applicant acknowledges that a complete copy of Nolan was provided to the Applicant's representative during the interview. The complete copy of the reference will be studied for its relevance and additional comments will be provided if possible.
>
> Nevertheless, it 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.
>
> Regarding new claims 41-60, even if one skilled in the art would have been motivated to modify the Gamache et al. composition in view of ISTA and Nolan, the artisan would have still obtained a 5-HT agonist composition, which is excluded from the amended claims by the "consisting essentially of" transitional phrase.

Id., p. 15-17.

With respect to the 35 U.S.C. § 103(a) rejection of claims 19-30 as obvious over Yakuji Nippo and U.S. Patent No. 6,369,112 to Xia, Applicants asserted that:

> As stated in the rejection, the Yakuji reference teaches a bromfenac solution. It does not teach tyloxapol. Xia teaches adding tyloxapol to a contact lens solution to improve stability of the solution.
>
> However Xia teaches adding tyloxapol to the contact lens solution for the purpose of improving stability of the biguanide disinfection agent in the solution. See the abstract and column 1, lines 10-12.
>
> On the other hand, the claimed invention does not contain a biguanide. Furthermore the preparation of Yakuji contains bromfenac and does not contain any biguanide, according to the partial translation of record. Bromfenac is structurally very different from a biguanide.
>
> 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., p. 17.

With respect to the 35 U.S.C. § 103(a) rejection of claims 19-38 as obvious over Yakuji Nippo and Nolan, Applicants asserted that:

> The teachings of Yakuji and Xia are discussed above. Nolan (abstract) fails to remedy the deficiencies of Yakuji and Xia. There is no teaching or suggestion in the cited references for combining tyloxapol, or any alkyl aryl polyether alcohol type polymer or polyethylene glycol fatty acid ester, with bromfenac, or a 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, to obtain the claimed preparation.

Id., p. 18.

With respect to the provisional non-statutory double patenting rejection, Applicants requested that the rejection be held in abeyance.

x) Non-Final Office Action Mailed July 18, 2008

In a Non-final Office Action mailed on July 18, 2008, the Examiner withdrew claims 61 and 62 as being drawn to a nonelected invention.

The Examiner also maintained the rejection of claims 19-29, 31-34, 36-38, 41-51, 53-56, 58-60, and 63 under 35 U.S.C. § 103(a) as obvious over Gamache and ISTA Pharmaceuticals news release. Specifically, the Examiner stated that:

> 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-$HT_{1B/1D}$ agonists with one or more anti-inflammatory agents, dosed concurrently or sequentially with anti-inflammatory agent compositions. (p. 12, lines 9-11); bromfenac is clearly taught as an anti-inflammatory compound specie[s] (p. 12, line 17; claim 11). This implies two different compositions as embodiments: 1) a composition containing a 1B/1D agonist and an anti-inflammatory agent (such as in claims 7, 10-11) and 2) two different compositions, where the first contains only an anti-inflammatory agent as the active compound, the second contains only a 1B/1D agonist as active agent (implied by sequential dosing). Taking Example 4 as the model formulation, it would have been obvious to one of ordinary skill in the art at the time of the invention to substitute bromfenac for Moxifloxin taught in the example, giving an aqueous liquid preparation containing both required ingredients of the instant claims, bromfenac and tyloxapol (along with the 5-HT1 B/1 D agonists). Alternatively, it would have been obvious to substitute bromfenac for both Moxifloxin and the 1B/1D agonist, giving an aqueous liquid preparation containing both required ingredients of the instant claims, bromfenac and tyloxapol (without a 5-HT1 B/1 D agonist). The motivation to prepare the combination formulation (with two active ingredients) would have

been for the treatment of otic inflammatory reactions and responses, taught by Gamache (on p. 12, lines 8-11). The motivation to prepare the single active formulation (without a 5-$HT_{1B/1D}$ agonist) would have been for the sequential treatment of otic inflammatory reactions and responses, taught by Gamache. The motivation to select bromfenac as the anti-inflammatory agent would have been the art-recognized usefulness for the purpose of treating inflammatory reactions and responses, recognized by Gamache, and bomfenac sodium at the concentrations of the claims is taught by ISTA Pharmaceuticals and Nolan, also suitable for the purpose of Gamache's formulations. With respect to the tyloxapol concentrations recited in instant claims 25 and 32, of "about 0.02 w/v %" and "about 0.3 w/v%", the amount taught is considered to be close, if not within the unspecified range implied by "about". Alternatively, it would have been obvious to optimize concentrations of tyloxapol, which one of ordinary skill in the art would have recognized is a surfactant, to optimize the conditions of the formulations for solubility of other ingredients, stability and efficacy in the anti-inflammatory action of the formulation, which would have given tyloxapol concentrations of the instant claims. The motivation would have been the routine optimization of conditions.

Applicant argues that ISTA Pharmaceuticals press release about Xibrom has a different composition than the instant formulation. This point is not at issue; the reference was cited to demonstrate salts and hydrates of bromfenac and concentrations of the instant claims. Applicant also argues the ISTA reference of the Nolan reference in combination with Gamache does not suggest the claimed invention comprising the at least two components. This is not persuasive because Gamache alone suggests the combination of the two required components, as outlined above. Applicant argues that the combination of a 1B/1D agonist with bromfenac would not read on claims 41-60 because of the recitation of the "consisting essentially of" transitional phrase. This is not persuasive, since the phrase "at least" after "consisting essentially of" in claim 41 opens the subject matter to any additional ingredients. Even if the "at least" were absent from the claim language, the embodiment suggested by Gamache of only one single active anti-inflammatory agent (useful in a sequential treatment method) would obviate such a claim construction. With respect to claim 63, even if the "comprising" language was replaced by "consisting of" language, the substitution of bromfenac for the active ingredients in Example 4 as suggested by Gamache would produce a composition that reads on the specific components recited in claim 63, assuming water would be required in that claim.

Non-final Office Action, p. 3-6.

Claims 41-60 and 63 were rejected under 35 U.S.C. § 112, second paragraph as indefinite. In particular, the Examiner stated that:

> With respect to claims 41-60, the recitation of the transitional phrase generally considered to refer to closed claim language, "consisting essentially of" together with the open language term, "at least" in the 1st line of claim 41, is not clear whether open construction or closed construction is meant by the claim; additionally the language of the 1st and 2nd components, "comprising", an open construction term is also unclear and inconsistent with the closed construction phrase, "consisting essentially of'. It is not clear whether formulations containing the recited components and additional components would fall within or outside of the metes and bounds of the instant claims. For other rejections the phrase "consisting essentially of at least" is construed to have the same meaning as "comprising", consistent with the broadest reasonable interpretation of these claims.
>
> With respect to claim 63, the recitation of the transitional phrase, "consisting of the two components, each of which use the term, "comprising" to recite the compounds present in each components, does not make clear whether the claim construction is closed or open; i.e., it is not clear whether a formulation containing one compound from the 1st component, one compound from the 2nd component, one or more of the optional components recited and at least one non-component compound (not recited in the claim), such as water or an alcohol, would fall within the scope of or be excluded from the subject matter of the claim. For prior art rejections, the claims are construed in the broader meaning, i.e., the presence of "comprising" in the claim has the meaning of open ended claim construction.
>
> Additionally, claim 63 recites "an aqueous liquid preparation" consisting of two required components, and optionally containing at least one additional component, none of the required or optional components recite water. The presence of an "aqueous" preparation along with the absence of water is inconsistent, and does not make clear whether water is required, optional or absent.

Id., p. 7-8.

The Examiner also rejected claims 19-38, 41-60, and 63 under 35 U.S.C. § 103(a) as obvious over U.S. Patent No. 5,998,465 to Hellberg *et al.* ("Hellberg") and Nolan. Specifically, the Examiner stated that:

> Hellberg teaches pharmaceutical compositions of anti-inflammatory compounds (abstract); the compounds include a non-steroidal anti-inflammatory moiety (NSAIA) and an antioxidant moiety linked through an ester bond formed by the carboxylic acid moiety of the

> NSAIA (col. 2, lines 20-24); NSAIA moieties include bromfenac (col. 3, line 57; claim 5); examples 2 and 3 (col. 11) teach topical ophthalmic formulations useful for treating inflammation, both of these formulations include tyloxapol at 0.01-0.05 w/v %, HPMC (thickener), benzalkonium chloride (preservative), edetate disodium (chelating agent) (col. 11, Examples 2-3); the pH is adjusted to 7.4 (about 7.5; col. 11, line 64); topical formulations administered by drops (eyedrops; col. 10, lines 15-18). Hellberg does not teach bromfenac (only the ester of bromfenac). Nolan teaches bromfenac (the sodium salt, sesquihydrate form) was effective as a topical analgesic at concentrations of 0.1-0.32 (:)/0 in mice and more potent than the other drugs tested (abstract). 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 in the example formulation giving formulations of the instant claims and to select concentrations of bromfenac sodium, sesquihydrate of 0.1, about 0.2 and about 0.32 %, in the invention of Gamache, since these values have demonstrated efficacy for topical use. It would also have been obvious to adjust the concentration of tyloxapol, to optimize the formulations for the effect would on the solubility and stability of the aqueous preparations, which would have resulted in the effective tyloxapol concentrations of about 0.02 and 0.3 w/v%, recited in claims 25 and 32. The motivation to substitute bromfenac in the Hellberg formulations would have bee the art-recognized equivalent activity of bromfenac as an anti-inflammatory agent in topical usage. The motivation to adjust concentrations would have been the routine optimization of these topical ophthalmic formulations for anti-inflammatory use in the eye.

Id., p. 8-9.

The Examiner also rejected claims 41-60 under 35 U.S.C. § 101 as substantial duplicates over claims 19-38. Specifically, the Examiner stated that:

> This objection is necessitated by the amendment adding new claims. Claim 41 uses the transitional phrase in the preamble, "consisting essentially of at least", whereas claim 19 uses the transitional phrase, "comprising"; all other wording is identical. "Consisting essentially of" is generally closed language, excluding components not recited in the claim. However, the presence of the open language term, "at least" removes the closed language of "consisting essentially of', giving the meaning that the recited components are required, but additional components no recited may optionally be present, which is the same meaning possessed by the term, "comprising". Therefore, though the two sets of claims use slightly different wording, the meanings are the same.

Id., p. 10.

The Examiner also maintained the provisional non-statutory rejection of claims 19-38, 41-60, and 63 over copending application, Appl. Ser. No. 11/755,662.

xi) Interview Summary Mailed December 23, 2008

In an Interview Summary mailed on December 3, 2008, the Examiner stated that an Interview with Applicants took place November 20, 2008 and that "Potential claim amendments were discussed that might potentially overcome the prior art-based rejections; potential designs of experimental studies were also discussed that might yield unexpected results to overcome the 103 rejections." *Interview Summary.*

xii) Applicants' Response Dated January 15, 2009

On January 15, 2009, Applicants filed an Amendment that cancelled claims 30, 35, 52, and 57 and amended claims 19, 39 (withdrawn), 40 (withdrawn), 41, and 61-63:

> 19. (Currently Amended) An aqueous liquid preparation comprising at least 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, wherein said liquid preparation is in the form of an eye drop.
>
> 39. (Withdrawn – Currently Amended) A method for stabilizing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof in an aqueous liquid preparation, which comprises incorporating tyloxapol or polyethylene glycol monostearate into an aqueous liquid preparation containing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, to obtain an aqueous liquid preparation comprising at least 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 tyloxapol or pelyethylene glycol monostearate, wherein said liquid preparation is in the form of an eye drop.
>
> 40. (Withdrawn – Currently Amended) A method for inhibiting decrease in preservative effect of a preservative in an aqueous liquid preparation of 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, which comprises incorporating tyloxapol or polyethylene glycol monostearate into an aqueous liquid preparation containing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof and a preservative, to obtain an aqueous liquid preparation comprising at least 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 tyloxapol or pelyethylene glycol monostearate, wherein said liquid preparation is in the form of an eye drop.

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-(4- bromobenzoyl)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 in the form of an eye drop.

61. (Withdrawn – Currently Amended) A method for stabilizing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof in an aqueous liquid preparation, which comprises incorporating tyloxapol or polyethylene glycol monostearate into an aqueous liquid preparation containing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, to obtain an aqueous liquid preparation consisting essentially of at least 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 tyloxapol or polyethylene glycol monostearate, wherein said liquid preparation is in the form of an eye drop.

62. (Withdrawn – Currently Amended) A method for inhibiting decrease in preservative effect of a preservative in an aqueous liquid preparation of 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, which comprises incorporating tyloxapol or polyethylene glycol monostearate into an aqueous liquid preparation containing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof and a preservative, to obtain an aqueous liquid preparation consisting essentially of at least 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 tyloxapol or polyethylene glycol monostearate, together with a preservative, wherein said liquid preparation is in the form of an eye drop.

63. (Currently Amended) 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, wherein said liquid preparation is in the form of an eye drop.

Applicants remarked that the amendments were made as per the discussion of the interview held November 20, 2008.

With respect to the rejection of claims 19-29, 31-34, 36-38, 41-51, 53-56, 58-60, and 63 as obvious over Gamache *et al.* and ISTA Pharmaceuticals or Nolan, Applicants asserted that the amended claims overcame the rejection:

> Claims 19, 39, 40, 41, 61, 62 and 63 have been amended to require that the aqueous liquid preparation is in the form of an eye drop according to claims 30, 35, 52 and 57. None of claims 30, 35, 52 or 57 were encompassed by the rejection.
>
> Accordingly this ground of rejection is deemed to be overcome.

Response, p. 11.

Applicants also provided additional remarks to a potential § 103 rejection based on a different combination of references:

> The subject matter of the claimed invention is directed to an eye drop having a 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.
>
> On the other hand, Gamache et al. do not disclose or suggest this specific combination. The cited reference is directed to compositions comprising of 5-HT_{1D} and/or HT_{1B} agonists. The cited reference states that these agonists may be combined with an extensive list of other pharmaceutical agents, i.e. (1) anti-microbial agent, (2) anti-inflammatory agents or (3) anti-allergy agent (please see page 6, lines 1-3 of Gamache). Gamache et al. only describes "bromfenac" as one of many examples of anti-inflammatory agents enumerated on page 12, lines 11-24. Gamache et al. does not concretely describe nor suggest the claimed preparation containing bromfenac.
>
> Further, tyloxapol (0.05% w/v) is only mentioned as being added to an 1B/1D agonist (0.1-1.0% w/v) and moxifloxacin (0.3% w/v) in Example 4 (an Example of an otic/nasal suspension). There is no explanation about tyloxapol in the description of Gamache et al. or why it is included. Moreover in this Example, moxifloxacin is incorporated as a well-known antibacterial agent but 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 1B/1D 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.

Further, Gamache et al. is silent about an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester component according to the claimed eye drop.

Thus the disclosure of Gamache et al. would suggest to the skilled artisan thousands of possible combinations of ingredients to include with an IB/ID agonist. Such disclosure does not lead the artisan to the claimed specific combination nor does such disclosure render the claimed combination obvious. The prior art must motivate one skilled in the art to make the claimed combination. There is no teachings or suggestion in Gamache of selecting bromfenac in combination with an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester.

Furthermore, Gamache et al. is directed to compositions for relieving otic pain (abstract) by apply the compositions to the ear or nasally (page 10, lines 6-9 and Example 4). There is no teaching or motivation to make the claimed eye drop.

Regarding claims 41-51, 53-56 and 58-60, the claims are directed to an eye drop which consists essentially of the recited specific combination of ingredients. The claim recites the transitional phrase "consisting essentially of means that the claim is open to include the specified ingredients and additional ingredients 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 IB/ID agonist of the Gamache composition would affect the basic novel properties of the claimed preparation.

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. An IB/ID agonist is excluded from claims 41-51, 53-56 and 58-60 by the "consisting essentially of transitional phrase.

Regarding claim 63, the claim is limited to an eye drop which "consists of the recited bromfenac, recited an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester, and water. Such claim explicitly excludes other ingredients, such as an IB/ID agonist.

> For the foregoing reasons, Applicant submits that the present invention is unobvious from Gamache et al. and ISTA or Nolan to those skilled in the art.

Id., p. 11-13 (emphasis in original).

With respect to the 35 U.S.C. § 112, second paragraph rejection of claims 41-60 and 63 as indefinite, Applicants stated that "Based upon the Examiner's remarks during the personal interview, it is believed that this ground of rejection is overcome by the foregoing amendments." *Id., p. 3.*

With respect to the 35 U.S.C. § 103(a) rejection of claims 19-38, 41-60, and 63 as obvious over Hellberg and Nolan, Applicants traversed and stated that Hellberg required compounds with both anti-inflammatory and antioxidant activity:

> The Examiner asserts that it would have been obvious to substitute the compounds having anti-inflammatory and anti-oxidant activity used in the ophthalmic compositions of Hellberg et al. with bromfenac used in the dermal applications disclosed in Nolan et al. Applicants respectfully disagree.
>
> The intended purpose of the invention disclosed in Hellberg et al. is to provide "[c]ompounds having anti-inflammatory ***and*** antioxidant activity." See Hellberg et al., Abstract (emphasis added); see also Hellberg at column 2, lines 13-18 ("***The present invention provides*** new compounds having potent anti-inflammatory and anti-oxidant activity.") (emphasis added). Indeed, Hellberg et al. explicitly state that the principle of operation of the anti-inflammatory and antixodixant compounds is to provide a two-pronged therapeutic approach not previously available in the art:
>
> > The compounds of the present invention are capable of protecting against cellular damage by a wide range of insults. Since the compounds provide this protection by decreasing free radical or oxidative damage, reducing cyclooxygenase or lipoxygenase mediated inflammation, and improving site delivery, this therapy represents an improved two-pronged approach to cytoprotection.
>
> See Hellberg et al. at Column 2, lines 57-63. Therefore, the intended purpose of the invention disclosed in Hellberg et al. is to provide compounds with not only anti-inflammatory activity, but also anti-oxidant activity for improved therapeutic functionality:
>
> > The compounds also include an anti-oxidant component. As oxidative stress has been implicated in inflammatory responses, the presence of an anti-oxidant

> will further help treat the target tissue. The compounds of the present invention also exhibit properties present only in the combined molecule, not in the individual components. One such property is the inhibitory efficacy against 5-lipoxygenase, an enzyme known to be involved in inflammation.

See Hellberg et al. at Column 2, lines 38-45 (emphasis added).

Id., p. 14 (emphasis in original).

Applicants further argued that the proposed substitution with dual action anti-inflammatory and anti-oxident compounds disclosed in Hellberg with bromfenac would render the Hellberg invention unsatisfactory:

> Here, the Examiner asserts that it would have been obvious to substitute the anti-inflammatory and anti-oxidant compounds disclosed in Hellberg et al. with bromfenac as disclosed in Nolan et al. because of "the art recognized equivalent activity of bromfenac as an anti-inflammatory agent in topical usage." See Official Action date July 18, 2008 at page 9. But as indicated in the Official Action and in Hellberg et al., bromfenac is an anti-inflammatory and not an antioxidant. The proposed substitution of the dual action anti-inflammatory and anti-oxidant compounds disclosed in Hellberg et al. with bromfenac would render the Hellberg et al. invention unsatisfactory for its intended purpose of providing "compounds having potent anti-inflammatory and anti-oxidant activity." The proposed substitution would result in a bromfenac composition having only anti-inflammatory activity. This proposed modification would radically change the principle of operation of Hellberg et al. from "an improved two-pronged approach to cytoprotection" to a mere one-pronged approach based on anti-inflammatory action alone.
>
> Therefore, because the proposed substitution of the anti-inflammatory and anti-oxidant compounds disclosed in Hellberg et al. with bromfenac as disclosed in Nolan et al. would render the Hellberg et al. invention unsatisfactory for its intended purpose and radically change theprinciple of operation of Hellberg et al., Applicants respectfully submit a prima facie case of obviousness cannot be based on the combination of Hellberg et al. and Nolan et al.

Id., p. 15.

Applicants also argued that Hellberg taught away from the claimed invention:

> Applicants submit that Hellberg et al. explicitly teach away from the use of a compound, such as bromfenac, having only anti-inflammatory

activity. Hellberg et al. clearly recite deficiencies in the use of non-steroidal anti-inflammatory agents such as bromfenac:

> Non-steroidal anti-inflammatory agents (NSAIA) have been used for the treatment of inflammatory disorders. The following references may be referred to for further background concerning this use of NSAIAs:
>
> Ophthalmoscope, volume 8, page 257 (1910);
>
> FASEB Journal, volume 1, page 89 (1987); and
>
> Inflammation and Mechanisms and Actions of Traditional Drugs, vol. I Anti-inflammatory and Anti-rheumatic drugs. Boca Raton, Fla., CRC Press, (1985).
>
> However, ***there are some problems associated with NSAIA treatment including delivery to the appropriate site of action and side effects*** (Goodman and Gilman's The Pharmacological Basis of Therapeutics, pages 638-669, Pergman Press, NY (1990)).

See Hellberg et al. at Column 1, lines 28-37 (emphasis added).

* * *

Here, Hellberg et al. plainly state that NSAIA treatment is associated with "problems" such as "side effects" and "delivery to the appropriate site of action." In light of this teaching away from the use of a non-steroidal anti-inflammatory agent (NSAIA), one skilled in the art would not substitute bromfenac, a known NSAIA, for the anti-inflammatory and anti-oxidant compounds disclosed in Hellberg et al. Therefore, because Hellberg et al. teach away from the use of bromfenac, Applicants respectfully submit a prima facie case of obviousness cannot be based on the combination of Hellberg et al. and Nolan et al.

Id., p. 15-16 (emphasis in original).

With respect to the provisional non-statutory double patenting rejection, Applicants requested that the rejection be held in abeyance.

xiii) Final Rejection Mailed June 3, 2009

In a Final Office Action mailed on June 3, 2009, the Examiner maintained the rejection of claims 19-29, 31-34, and 36-38 under 35 U.S.C. § 103(a) as obvious over Gamache and ISTA Pharmaceuticals news release or Nolan. Specifically, the Examiner stated that:

> Applicant asserts that Gamache et al. in view of ISTA or Nolan et al. does not teach the claimed invention because the amended claims require that the aqueous liquid preparation is in the form of an eye drop. In response, please see the rejection supra regarding claims drawn to the composition "in the form of an eye drop". Further, Gamache teaches the composition to be employed intranasally and intraotically. There is nothing differentiating the composition of the instant claims from the composition of Gamache other than the claim that it is "in the form of an eye drop". Drops that are formulated for intranasal use and otic use are sterile and isotonic. The intended use must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. Since the drops of Gamache are capable of performing the intended use, then it meets the claim. Regarding the inclusion of other agents in the drops of Gamache, The claim language comprising leaves the claim open for the inclusion of unspecified ingredients, even in major amounts. Applicant asserts that the tyloxapol is only mentioned as being added to an 1B/1D agonist and moxifloxacin in example 4 with no explanation of why it is included. In response, a reference is not limited to working examples. *In re Fracalossi* 215 USPQ 569 (CCPA 1982). Applicant asserts that Gamache et [al.] is silent regarding the alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester component according to the claimed eye drop. In response, Gamache et al. teach polysorbate 20, 60, and 80 as a surfactant or co-solvent (see page 12).

Final Office Action, p. 8-9.

The Examiner also maintained the rejection of claims 19-29, 31-34, 36-38, 41-51, 53-56, 58-60, and 63 under 35 U.S.C. § 103(a) as obvious over Hellberg and Nolan. Specifically, the Examiner stated that:

> Applicant asserts that the intended purpose of the invention disclosed in Hellberg et al. is to provide compounds having anti-inflammatory activity and antioxidant activity and further asserts it would not be obvious to substitute bromfenac. In response, bromfenac is clearly disclosed as a compound that is contemplated for use in the invention of Hellberg et al. (see claims 5 and 19 of the patent). "Products of identical chemical composition (i.e. bromfenac) can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims (i.e. anti inflammatory and antioxidant activity) are necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990) (Applicant argued that the claimed composition was a pressure sensitive adhesive containing a tacky polymer while the product of the reference was hard and abrasion resistant. "The Board correctly found

> that the virtual identity of monomers and procedures sufficed to support a prima facie case of unpatentability of Spada's polymer latexes for lack of novelty.").
>
> In response to applicant's argument that Hellberg et al. is nonanalogous art, it has been held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). In this case, Hellberg et al. teach a composition for intraocular administration comprising inter alia, a compound (bromfenac) and tyloxapol (see examples).

Id., p. 9-10.

The Examiner also rejected claims 19-29, 31-34, 36-38, 41-51, 53-56, 58-60, and 63 under 35 U.S.C. § 112, second paragraph as indefinite. Specifically, the Examiner stated that:

> Claims 19 and 41 recite an aqueous liquid preparation comprising at least 2-amino-3-(4-bromobenzoyl)phenylacetic acid (bromfenac) and an alkyl aryl polyether alcohol type polymer or polyethylene glycol fatty acid ester "wherein said liquid preparation is in the form of an eye drop". It is unclear what is meant by "in the form of an eye drop. Is this aqueous liquid preparation in a container shaped like an eye drop? It is suggested that the claim be amended to recite "wherein said liquid preparation is formulated for ophthalmic administration".

Id., p. 3.

The Examiner also maintained the provisional non-statutory rejection of claims 19-38, 41-60, and 63 over copending application, Appl. Ser. No. 11/755,662.

xiv) Applicants' Response and Request for Continued Examination Dated October 5, 2009

On October 5, 2009, Applicants filed an Amendment that amended claims 19, 39 (withdrawn), 40 (withdrawn), 41, and 61-63:

> 19. (Currently Amended) An aqueous liquid preparation comprising at least 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, wherein said liquid preparation is formulated for ophthalmic administration ~~in the form of an eye drop~~.

39. (Withdrawn – Currently Amended) A method for stabilizing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof in an aqueous liquid preparation, which comprises incorporating tyloxapol or polyethylene glycol monostearate into an aqueous liquid preparation containing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, to obtain an aqueous liquid preparation comprising at least 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 tyloxapol or pelyethylene glycol monostearate, wherein said liquid preparation is formulated for ophthalmic administration ~~in the form of an eye drop~~.

40. (Withdrawn – Currently Amended) A method for inhibiting decrease in preservative effect of a preservative in an aqueous liquid preparation of 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, which comprises incorporating tyloxapol or polyethylene glycol monostearate into an aqueous liquid preparation containing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof and a preservative, to obtain an aqueous liquid preparation comprising at least 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 tyloxapol or pelyethylene glycol monostearate, wherein said liquid preparation is formulated for ophthalmic administration ~~in the form of an eye drop~~.

41. (Currently Amended) An aqueous liquid preparation consisting essentially of the following two components, wherein the first component comprising is 2-amino-3-(4- bromobenzoyl)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 ~~in the form of an eye drop~~.

61. (Withdrawn – Currently Amended) A method for stabilizing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof in an aqueous liquid preparation, which comprises incorporating tyloxapol or polyethylene glycol monostearate into an aqueous liquid preparation containing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, to obtain an aqueous liquid preparation consisting essentially of at least 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 tyloxapol or polyethylene glycol monostearate, wherein said liquid preparation is formulated for ophthalmic administration ~~in the form of an eye drop~~.

[redacted]

62. (Withdrawn – Currently Amended) A method for inhibiting decrease in preservative effect of a preservative in an aqueous liquid preparation of 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, which comprises incorporating tyloxapol or polyethylene glycol monostearate into an aqueous liquid preparation containing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof and a preservative, to obtain an aqueous liquid preparation consisting essentially of at least 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 tyloxapol or polyethylene glycol monostearate, together with a preservative, wherein said liquid preparation is formulated for ophthalmic administration ~~in the form of an eye drop~~.

63. (Currently Amended) 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, wherein said liquid preparation is formulated for ophthalmic administration ~~in the form of an eye drop~~.

Applicants remarked that the claims were amended as suggested by the Examiner in the Office Action dated June 3, 2009. *Response, p. 10.* In the response, Applicants also made reference to an upcoming interview with the Examiner scheduled on October 7, 2009.

xv) Interview Summary Mailed October 8, 2009

In an Interview Summary mailed on October 8, 2009, the Examiner stated that an Interview with Applicants took place October 7, 2009 and that "Hellberg teaches any NSAIA including bromfenac covalently linked to an antioxidant. Applicants presented arguments that there is no motivation to replace the Hellberg compound with the Nolan compound." *Interview Summary.*

xvi) Non-Final Office Action Mailed December 24, 2009

In a Non-final Office Action mailed on December 24 2009, the Examiner maintained the rejection of claims 19-29, 31-34, 36-38, 41-51, 53-56, 58-60, and 63 under 35 U.S.C. § 103(a) as obvious over Hellberg and Nolan. Specifically, the Examiner stated that:

> Hellberg teaches pharmaceutical compositions of anti-inflammatory compounds (abstract); the compounds include a non-steroidal anti-inflammatory moiety (NSAIA) and an antioxidant moiety linked through an ester bond formed by the carboxylic acid moiety of the NSAIA (col. 2, lines 20-24); NSAIA moieties include bromfenac (col. 3, line 57; claim 5); examples 2 and 3 (col. 11) teach topical ophthalmic formulations useful for treating inflammation, both of

these formulations include tyloxapol at 0.01-0.05 w/v %, HPMC (thickener), benzalkonium chloride (preservative), edetate disodium (chelating agent) (col. 11, Examples 2-3); the pH is adjusted to 7.4 (about 7.5; col. 11, line 64); topical formulations administered by drops (eye drops; col. 10, lines 15-18). Hellberg does not teach bromfenac (only the ester of bromfenac). Nolan teaches bromfenac (the sodium salt, sesquihydrate form) was effective as a topical analgesic at concentrations of 0.1-0.32 (:)/0 in mice and more potent than the other drugs tested (abstract). 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 in the example formulation giving formulations of the instant claims and to select concentrations of bromfenac sodium, sesquihydrate of 0.1, about 0.2 and about 0.32 %, in the invention of Gamache, since these values have demonstrated efficacy for topical use. It would also have been obvious to adjust the concentration of tyloxapol, to optimize the formulations for the effect would on the solubility and stability of the aqueous preparations, which would have resulted in the effective tyloxapol concentrations of about 0.02 and 0.3 w/v%, recited in claims 25 and 32. The motivation to substitute bromfenac in the Hellberg formulations would have bee the art-recognized equivalent activity of bromfenac as an anti-inflammatory agent in topical usage. The motivation to adjust concentrations would have been the routine optimization of these topical ophthalmic formulations for anti-inflammatory use in the eye.

Non-final Office Action, p. 3-4.

Examiner also maintained the rejection of claims 19-29, 31-34, and 36-38 under 35 U.S.C. § 103(a) as obvious over Gamache and ISTA Pharmaceuticals news release or Nolan. Specifically, the Examiner stated that:

Gamache teaches compositions for otic and intranasal use (p.6, lines 5-6) that contain a combination of a 5-HT agonist and an anti-inflammatory agent (p. 6, lines 1-4; p. 12 lines 9-10) or alternatively sequential or concurrent dosing of separate compositions that contain the 5-HT antagonist in one composition and the anti-inflammatory agent in a second composition (p. 12, lines 9-11); specifically claimed is the anti-inflammatory specie bromfenac (2-amino-3-(4-bromobenzoyl)phenylacetic acid). 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; p. 13, lines 6-8); aqueous formulations are preferred (p. 10, lines 11-14); tyloxapol is taught in a concentration of 0.05 (:)/0 (w/v) (p. 16, line 30). It is noted that instant claim 21 and further dependent claims limit the options for the salt of bromfenac to the sodium salt, and that the specific concentrations recited in dependent claims apply to the sodium salt; the other options

(bromfenac or a hydrate of bromfenac) are still viable choices that are part of instant claim 21 claims depending therefrom (which depend on and include the options of claim 20). Gamache teaches bromfenac in the concentration range of claim 20 (which is also an option of claims 21-24 and 31). The salt form of bromfenac in solution will be the same when the acid is dissolved in a solution followed by adjustment to the desired pH with NaOH/HCI (Gamache, p. 15, line 33) as when the sodium salt is dissolved in solution adjusted to the same pH; in this case Gamache also teaches the sodium salt limitation of instant claim 21, albeit not the sodium salt concentration limitation of instant claim 22 and further dependent claims, since the claim is drawn to an aqueous liquid preparation, irrespective of how it is prepared. However, the concentration range of 0.01-1.0% overlaps and encompasses the claimed concentration range of the sodium salt of bromfenac instantly claimed.

The ISTA Pharmaceuticals news release demonstrates that products containing 0.1 (:)/0 bromfenac sodium acquired US marketing rights for Xibrom in May 2002 (were known by others in this country before applicant's priority date, a 35 USC 102(a) date). Nolan teaches bromfenac (the sodium salt, sesquihydrate form) was effective as a topical analgesic at concentrations of 0.1-0.32 (:)/0 in mice and more potent than the other drugs tested (abstract). 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, sesquihydrate of 0.1, about 0.2 and about 0.32 %, in the invention of Gamache, since these values have demonstrated efficacy for topical use. It would have been obvious to adjust the concentration of tyloxapol, to see what the effect would be on the solubility and stability of the aqueous preparations, which would have resulted in the effective concentrations of the instant claims. 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, in a more aqueous soluble ionic form. The motivation would have been to prepare pharmaceutical products with optimal drug dosage and stability.

Id., p. 4-6.

The Examiner also maintained the provisional non-statutory rejection of claims 19-38, 41-60, and 63 over copending application, Appl. Ser. No. 11/755,662.

xvii) Applicants' Response Dated March 24, 2010

On March 24, 2010, Applicants filed an Amendment that cancelled claims 19-40 and 63; amended claims 41-45, 47, 48, 51, 54, 61, and 62; and added new claims 64-68:

41. (Currently Amended) An aqueous liquid preparation consisting essentially of the following two components, wherein the first component ~~comprising~~ is 2-amino-3-(4- bromobenzoyl)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.

42. (Currently Amended) The aqueous liquid preparation according to claim 41, wherein the ~~alkyl aryl polyether alcohol type polymer~~ second component is tyloxapol~~; wherein the concentration of the tyloxapol is selected from a range of about 0.01 w/v % to about 0.5 w/v %; and wherein the concentration of the 2-amino-3-(4 bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof is selected from a range of about 0.01 to about 0.5 w/v %~~.

43. (Currently Amended) The aqueous liquid preparation according to claim ~~42~~41, wherein the first component is ~~pharmacologically acceptable salt of~~ a 2-amino-3-(4-bromobenzoyl)phenylacetic acid ~~is a~~ sodium salt.

44. (Currently Amended) The aqueous liquid preparation according to claim ~~43~~41, wherein the second combonent is tyloxapol and the pharmacologically acceptable salt of 2-amino-3-(4-bromobenzoyl)phenylacetic acid is a sodlium salt, wherein the concentration of the tyloxapol is from about 0.01 w/v % to about 0.5 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 to about 0.2 w/v % ~~2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is selected from a range of about 0.05 to about 0.2 w/v %~~.

45. (Currently Amended) The aqueous liquid preparation according to claim 44, wherein the concentration of the tyloxapol is ~~selected~~ from ~~a range of~~ about 0.01 w/v % to about 0.3 w/v % and the concentration of th e2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.05 to about 0.2 w/v %.

47. (Currently Amended) The aqueous liquid preparation according to claim ~~46~~45, wherein the concentration of the tyloxapol is about 0.02 w/v %.

48. (Currently Amended) The aqueous liquid preparation according to claim ~~47~~41, wherein the formulation further includes one or more additives selected from the group consisting of a preservative, buffer, thickener, stabilizer, chelating agent, and pH controlling agent.

51. (Currently Amended) The aqueous liquid preparation according to claim ~~50~~49, wherein the pH is from about 7.5 to about 8.5.

54. (Currently Amended) The aqueous liquid preparation according to claim ~~53~~45, wherein the concentration of the tyloxapol is about 0.3 w/v %.

61. (Withdrawn – Currently Amended) A method for stabilizing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof in an aqueous liquid preparation, which comprises incorporating

[redacted]

tyloxapol or polyethylene glycol monostearate into an aqueous liquid preparation containing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, to obtain an aqueous liquid preparation consisting essentially of ~~at least~~ the following two components, the first component ~~comprising~~ being 2-amino-3-(4- bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and the second component ~~comprising~~ being tyloxapol or polyethylene glycol monostearate, wherein said liquid preparation is formulated for ophthalmic administration.

62. (Withdrawn – Currently Amended) A method for inhibiting decrease in preservative effect of a preservative in an aqueous liquid preparation of 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, which comprises incorporating tyloxapol or polyethylene glycol monostearate into an aqueous liquid preparation containing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof and a preservative, to obtain an aqueous liquid preparation consisting essentially of ~~at least~~ the following two components, the first component ~~comprising~~ being 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and the second component ~~comprising~~ being tyloxapol or polyethylene glycol monostearate, together with a preservative, wherein said liquid preparation is formulated for ophthalmic administration.

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,

(b) tyloxapol,

(c) boric acid,

(d) sodium tetraborate,

(e) EDTA sodium salt,

(f) benzalkonium chloride,

(g) polyvinylpyrrolidone, and

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

65. (New) The aqueous liquid preparation of claim 64, wherein (a) is a'2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt.

66. (New) The aqueous liquid preparation of claim 65, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.01 to about 0.5 w/v % and the concentration of the tyloxapol is about 0.02 w/v %.

67. (New) The aqueous liquid preparation of claim 66, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is about 0.01 w/v %.

68. (New) The aqueous liquid preparation of claim 66, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is about 0.1 w/v %.

Applicants made reference to an interview with the Examiner on February 10, 2010 and stated that the 103 rejection of claims 41 *et al.* would "likely to be withdrawn in view of the arguments presented in the interview, which arguments are essentially reiterated hereinbelow." *Response, p. 7.*

With respect to the 35 U.S.C. § 103(a) rejection of claims 19-29, 31-34, and 36-38 as obvious over Gamache *et al.* and ISTA Pharmaceuticals or Nolan, Applicants indicated that the rejection was overcome by the cancellation of all rejected claims.

With respect to the 35 U.S.C. § 103(a) rejection of claims 19-29, 31-34, 36-38, 41-51, 53-56, 58-60, and 63 as obvious over Hellberg and Nolan, Applicants traversed and reiterated the previous arguments that Hellberg required compounds with both anti-inflammatory and antioxidant activity. Applicants also asserted that the Hellberg compounds offered additional advantages:

> Moreover, the compounds of Hellberg et al. are intended to offer advantages not provided by the mere administration of individual agents such as bromfenac. Such intended advantages include a uniform delivery of an active molecule, simplifying issues of drug metabolism, toxicity and delivery, as well as 5-lipooxygenase inhibitory activity not present in the individual agents.
>
> > The use of a single agent having both activities over a combination of two different agents provides uniform delivery of an active molecule, thereby simplifying issues of drug metabolism, toxicity and delivery.
>
> See Hellberg et al. at Column 2, lines 7-10.
>
> > Additionally, the compounds of the present invention exhibit 5-lipoxygenase inhibitory activity not present in the individual compounds.
>
> See Hellberg et al. at Column 2, lines 16-18.
>
> > The compounds of the present invention also exhibit properties present only in the combined molecule, not in the individual components. One such property is the inhibitory efficacy against 5-lipoxygenase, at enzyme known to be involved in inflammation.
>
> See Hellberg et al. at Column 2, lines 41-44 (emphasis added).

[redacted]

An additional intended advantage of the Hellberg bifunctional ester compounds is disclosed at Col. 2, lines 46 to 56:

> Another advantage of the present invention is that the antiinflammatory moiety and the anit-oxidant moiety are linked through an ester bond. Since the carboxylic acid moiety of the NSAIA has been converted to an ester, the resultant molecule is neutrally charged, thus increasing lipohilicity and drug delivery.

Thus, the Hellberg bifunctional ester compounds are intended to increase lipophilicity and drug delivery relative to bromfenac alone.

Response, 8-9.

Applicants further argued that the proposed substitution with dual action anti-inflammatory and anti-oxident compounds disclosed in Hellberg with bromfenac would render the Hellberg invention unsatisfactory:

> Here, the proposed substitution of the Hellberg bifunctional anti-inflammatory, antioxidant ester compounds with bromfenac would render the Hellberg et al. invention unsatisfactory for its intended purpose of providing "compounds having potent anti-inflammatory and anti-oxidant activity" with increased "lipophilicity and drug delivery" and "5-lipoxygenase inhibitory activity not present in the individual compounds." Applicant respectfully submits that this proposed modification would radically change the principle of operation of Hellberg et al. from "an improved two-pronged approach to cytoprotection" to a mere one-pronged approach based on anti-inflammatory action alone.
>
> Therefore, because bromfenac is not equivalent to the Hellberg bifunctional ester compounds and because the proposed substitution would render the Hellberg et al. invention unsatisfactory for its intended purpose and radically change the principle of operation of Hellberg et at, Applicant respectfully submits a prima fa,cie case of obviousness cannot be based on the combination of Hellberg et al. and Nolan et al.

Id., p. 9.

Applicants also argued that Hellberg taught away from the claimed invention by reiterating the same arguments as in the previous response as well as referring to U.S. Patent No. 5,886,030:

> See also U.S. Patent No. 5,886,030, a copy of which is enclosed, which states:

> Stinging and burning sensations, as well as general discomfort, are often associated with the topical ophthalmic application of certain types of ophthalmic agents. It is believed that such ocular discomfort is due to the presence of certain functional groups in these agents. Examples of such agents which product ocular discomfort include, but are not limited to, 13-blockers such as betaxolol; prostaglandins and prostaglandin derivatives; muscarinics such as pilocarpine; a-adrenergics such as epinephrine, clonidine and apraclonidine; cholinergics such as carbochol; and nonsteroidal anti-inflammatory drugs ("NSAMS") such as diclofenac and suprofen.

See U.S. Patent No. 5,886,030 at Column 1, lines 21-32.

* * *

> Here, Hellberg et al. exclude the use of a single NSATA's by disclosing that such compounds are associated with "problems" such as "side effects" and "delivery to the appropriate site of action." In light of this teaching away from the use of a non-steroidal antiinflammatory agent (NSAIA), one skilled in the art would not substitute bromfenac, a known NSAIA, for the anti-inflammatory and anti-oxidant compounds disclosed in Hellberg et al. Therefore, because Hellberg et al. teach away from the use of bromfenac, Applicant respectfully submits a prima facie case of obviousness cannot be based on the combination of Hellberg et al. and Nolan et al.

Id., p. 10-11.

Applicants further argued that no motivation is present:

> In addition, one skilled in the art would not have been motivated along the lines of the claimed invention by Hellberg et al. The claimed invention uses the second component as a cosolvent to assist in stabilizing the bromfenac. The second component of the claimed invention is an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester, preferably tyloxapol.
>
> Hellberg et al., however, fail to list tyloxapol as a cosolvent. See column 9, lines 1-5. Instead, Hellberg et al, use tyloxapol for an entirely different purpose. Whereas bromfenac is relatively soluble, the bifunctional ester compounds of Hellberg et al. are relatively lipophilic and insoluble. According to Example 3 bridging columns 11-12, the tyloxapol is apparently used as a milling diluent to grind the relatively insoluble bifunctional ester compound of Hellberg et al. to improve the

> solubility of the more lipophilic Hellberg ester compounds. In addition, the tyloxapol apparently helps to prevent the ground bifunctional ester compounds from aggregating into larger particles. Therefore the only apparent reason that tyloxapol is used in the compositions of Examples 2 and 3 of Hellberg et al. is as a grinding and anti-aggregation agent for the relatively lipophilic insoluble bifunctional ester compounds of Hellberg et al. Hence one skilled in the art, reading Hellberg et al,, would not have been motivated to use tyloxapol in combination with bromfenac, because bromfenac does not suffer from the problems of lipophilicity and insolubility relative to the bifunctional ester compounds of Hellberg et al.

Id., p. 12.

With respect to the provisional non-statutory double patenting rejection, Applicants stated that all other grounds of rejection were believed to be overcome and respectfully requested withdrawal of the provisional rejection. *Id.*

xviii) Final Rejection Mailed June 24, 2010

In a Final Office Action mailed on June 3, 2009, the Examiner rejected claims 41 and 42 under 35 U.S.C. § 102(b) as anticipated by U.S. Patent No. 5,603,929 to Desai *et al.* ("Desai"). Specifically, the Examiner stated that:

> 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 (column 3, lines 13-29, claims 4 and 7) and polysorbates such as tweens and tyloxapol and further comprising boric acid buffer (column 2, lines 18-44).

Final Office Action, p. 2.

The Examiner also rejected claims 43-51, 53-56, 58-60, and 64-68 under 35 U.S.C. § 103(a) as obvious over Desai in fview of U.S. Patent No. 5,475,034 to Yanni *et al.* ("Yanni") and Hellberg. Specifically, the Examiner stated that:

> 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 (column 3, lines 13-29, claims 4 and 7) and polysorbates such as tweens and tyloxapol and further comprising boric acid buffer (column 2, lines 18-44). It does not teach the concentration of about 0.01`)/0 to about 0.5% w/v. Yanni et al. teach 2-amino-3-4-bromobenzoylphenylacetamide (compound 15, column 9) and teach topically administrable ophthalmic compositions such as solutions, gels or ointment in concentrations of from about 0.01 to about 0.5% preferably (column 15, lines 1-55). Yanni et al. teach tyloxapol but it

does not recite the specific amount. Hellberg et al. teach tyloxapol in an ophthalmic solution comprising NSAIA moieties include bromfenac (col. 3, line 57; claim 5); examples 2 and 3 (col. 11) in an amount of 0.01 to 0.05 (:)/0 w/v (see examples 2 and 3, column 11). Addressing instant claims 48, 49, 55, 56, 59 and 60 drawn to the addition of one or more additives selected from a preservative, buffer, thickener, stabilizer, chelating agent and pH controlling agent, Desai et al. teach preservatives such as boric acid (column 2, lines 18-22), and benzalkonium chloride (column 3, lines 30-35), viscosity modifying agents (thickeners) such as polyvinyl pyrrolidone (column 3, lines 46-57), chelating agents (column 3, line 43) and pH controlling agent such as sodium hydroxide (see formulation example 1, column 4). The pH is adjusted to 7.4 (see example 1, column 4) which is encompassed by instant claim 50 drawn to a pH of from about 7 to 9. Addressing instant claim 51, drawn to a pH from about 7.5 to about 8.5, Desai teach a pH of about 7.4 as noted supra. A prima facie case of obviousness exists where the claimed ranges and prior art ranges do not overlap but are close enough that one skilled in the art would have expected them to have the same properties. Titanium Metals Corp. of America v. Banner, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985). Addressing instant claim 64, 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 (column 3, lines 13-29, claims 4 and 7) and tyloxapol and further comprising boric acid buffer (a.k.a. sodium tetraborate) (column 2, lines 18-44), Benzalkonium chloride (column 3, line 34), polyvinyl pyrrolidone (column 3, line 52). It does not teach EDTA sodium salt and sodium sulfite, however, Yanni et al. teach ophthalmic solutions comprising 2-amino-3-4-bromobenzoylphenylacetamide (compound 15, column 9) and further teach incorporation of sulfites such as sodium (column 2, lines 12-14) and EDTA sodium salt (disodium EDTA) (see column 16, line 57 and column 17, line 5). It would have been obvious to employ said sodium sulfite and EDTA sodium salt in an ophthalmic formulation motivated by the teaching of Yanni et al. who disclose disodium EDTA and sodium sulfite in ophthalmic formulations of bromfenac for the purpose of stabilizing the solution (column 2, lines 2-14).

Id., p. 3-4.

The Examiner also maintained the provisional non-statutory rejection of claims 41-51, 53-56, 58-60, and 64-68 over copending application, Appl. Ser. No. 11/755,662.

xix) Applicants' Response and Request for Continued Examination Dated October 25, 2010

On October 25, 2010, Applicants filed an Amendment that amended claims 41, 61, 62, and 64:

41. (Currently Amended) An aqueous liquid preparation consisting essentially of the following two components, wherein the first component is 2-amino-3-(4-bromobenzoyl)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 ammnium compound is included in said liquid preparation, the quaternary ammonium compound is limited to benzalkonium chloride.

61. (Withdrawn – Currently Amended) A method for stabilizing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof in an aqueous liquid preparation, which comprises incorporating tyloxapol or polyethylene glycol monostearate into an aqueous liquid preparation containing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, to obtain an aqueous liquid preparation consisting essentially of the following two components, the first component being 2-amino-3-(4- bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and the second component being tyloxapol or polyethylene glycol monostearate, wherein said liquid preparation is formulated for ophthalmic administration, and wherein when a quaternary ammnium compound is included in said liquid preparation, the quaternary ammonium compound is limited to benzalkonium chloride.

62. (Withdrawn – Currently Amended) A method for inhibiting decrease in preservative effect of a preservative in an aqueous liquid preparation of 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, which comprises incorporating tyloxapol or polyethylene glycol monostearate into an aqueous liquid preparation containing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof and a preservative, to obtain an aqueous liquid preparation consisting essentially of the following two components, the first component being 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and the second component being tyloxapol or polyethylene glycol monostearate, together with a preservative, wherein said liquid preparation is formulated for ophthalmic administration, and wherein when a quaternary ammnium 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,

(b) tyloxapol,

(c) boric acid,

(d) sodium tetraborate,

(e) EDTA sodium salt,

(f) benzalkonium chloride,

(g) polyvinylpyrrolidone, and

(h) sodium sulfite, ~~and~~ wherein said liquid preparation is formulated for ophthalmic Administration, and wherein benzalkonium chloride is the only quaternary ammnium compound which is included in said liquid preparation.

With respect to the rejection of claims 41 and 42 as anticipated by Desai, Applicants stated that Desai stated that benzalkonium chloride was incompatible with NSAIDS:

> Desai et al. teach at column 1, lines 27-34 that:
>
> > Benzalkonium chloride is a widely used preservative in ophthalmic solutions. However, benzalkonium chloride and other quaternary ammonium compounds are generally considered to be incompatible with ophthalmic compositions of drugs with acidic groups, such as nonsteroidal antiinflammatory drugs ("NSAIDS"). These preservative [sic] lose their ability to function as they form complexes with the charged drug compounds.
>
> As recognized by the Examiner, bromfenac used in the claimed preparation is an acidic "NSAID" drug.
>
> Desai et al. further note at column 2, lines 1-5 that:
>
> > The use of POLYQUAD® and other polymeric quaternary ammonium compounds as a disinfectant and preservative in contact lens care and artificial tear solutions is known. See, for example, U.S. Pat. Nos. 5,037,647; 4,525,346; and 4,407,791.
>
> Desai et al. summarize the intended purpose of their invention at column 2, lines 18-30 as follows:
>
> > It has now been discovered that the use of a combination of a polymeric quaternary ammonium compound such as POLYQUAD® and boric acid in ophthalmic compositions of acidic drugs provides a storage-stable composition which has surprisingly good preservative efficacy. This preservative combination of

> a polymeric quaternary ammonium compound and boric acid is useful in ophthalmic compositions of acidic drugs such as prostaglandins, antifungals, antibactedals [sic], and diagnostic agents. This preservative combination is especially useful in ophthalmic solutions of drugs containing either a carboxyl group such as non-steroidal anti-inflammatory drugs (NSAIDS) or a sulfonamide group such as antibacterial drugs.

Desai et al. further mention at column 3, lines 30-38 that:

> The compositions of the present invention may additionally include other ophthalmically acceptable components such as .... other preservatives (e.g. benzalkonium chloride) ... tyloxapol...

Thus, Desai et al. teach away from using a quaternary ammonium compound such as benzalkonium chloride as a preservative with acidic NSAID drugs like bromfenac. Desai et al. teach that the problems with benzalkonium chloride and other quaternary ammonium compounds can be avoided by using certain polymeric quaternary ammonium compounds in combination with boric acid.

Hence, an essential component of the Desai composition is a polymeric quaternary ammonium compound.

However, the instant claims as amended require that, when the claimed liquid preparation includes a quaternary ammonium compound, the quaternary ammonium compound is limited to benzalkonium chloride.

Thus the polymeric quaternary ammonium compounds disclosed in Desai et al. are excluded from the amended claims.

Response, 7-9 (emphasis in original).

With respect to the rejection of claims 43-51, 53-56, 58-60, and 64-68 under 35 U.S.C. § 103 as obvious over Desai in view of Yanni and Hellberg, Applicants argued that:

> As discussed above, each independent claim 41, 61 and 62 has been amended to require that "when a quaternary ammonium compound is included in said liquid preparation, the quaternary ammonium compound is limited to benzalkonium chloride". In addition, independent claim 64, which requires benzalkonium chloride, has similarly been amended to require that "benzalkonium chloride is the only quaternary ammonium compound which is included in said liquid preparation".

Thus, the instant claims as amended require that, when the claimed liquid preparation includes a quaternary ammonium compound, the quaternary ammonium compound is limited to benzalkonium chloride.

On the other hand, Desai et al. teach away from using a quaternary ammonium compound such as benzalkonium chloride as a preservative with acidic NSAID drugs like bromfenac. Desai et al. teach that the problems with benzalkonium chloride and other quaternary ammonium compounds can be avoided by using certain polymeric quaternary ammonium compounds in combination with boric acid.

Hence, an essential component of the Desai composition is a polymeric quaternary ammonium compound. However the polymeric quaternary ammonium compounds disclosed in Desai et al. are excluded from the amended claims.

There is no motivation or suggestion in the cited prior art to modify the Desai composition to replace the polymeric quaternary ammonium compound taught in Desai et al. with benzalkonium chloride. The intended purpose of the invention disclosed in Desai et al., as mentioned above, is to provide a storage-stable ophthalmic composition for acidic NSAID drugs, like bromfenac, having good preservative efficacy. This preservative combination is a polymeric quaternary ammonium compound and boric acid.

* * *

Here, a substitution of the Desai polymeric quaternary ammonium compound with benzalkonium chloride would render the Desai et al. invention unsatisfactory for its intended purpose.

Applicant therefore respectfully submits a prima facie case of obviousness cannot be based on the combination of Desai et al. with Yanni et al. and Hellberg et al.

In addition to the argument that the proposed modification changes the principle operation and intended purpose of Desai et al., Applicant reiterates that Desai et al. explicitly teach away from the use of a quaternary ammonium compound, such as benzalkonium chloride, as the only quaternary ammonium compound in an ophthalmic solution for an acidic NSAID drug such as bromfenac.

Id., p. 9-10 (emphasis in original).

With respect to the provisional non-statutory double patenting rejection, Applicants stated that all other grounds of rejection were believed to be overcome and respectfully requested withdrawal of the provisional rejection. *Id.*

[redacted]

xx) Interview Summary Mailed January 20, 2011

In an Interview Summary mailed on January 20, 2011, the Examiner stated that an Interview with Applicants took place January 14, 2011 and that:

> Applicants' representative pointed out changes to the independent claims to limit the quaternary ammonium compound to benzalkonium chloride. This amendment would specifically exclude polymeric quaternary ammonium compounds, necessary for the composition of Desai et al. Desai et al. teaches away from benzalkonium chloride with ophthamic compositions of drugs with acidic groups such as NSAIDs because they lose their ability to function because they form complexes with the charged drug compounds (column 1, lines 27-34).

Interview Summary continuation sheet.

xxi) Non-Final Office Action Mailed May 6, 2011

In a Non-final Office Action mailed on May 6, 2011, the Examiner rejected claims 41-48, 50-51, 53-55, and 58-59 under 35 U.S.C. § 103(a) as obvious over Yanni *et al.* (5,475,034) in view of U.S. Patent No. 5,540,930 to Guy *et al.* ("Guy"). Specifically, the Examiner stated that:

> Yanni et al. teaches a composition comprising an active agent see specifically Preparation XV (3-benzoylphenylacetic acid derivatives, salts are known) in 0.01-0.5%, polysorbate 80 in 0.01°/o, benzalkonium chloride, disodium EDTA, monobasic sodium phosphate, dibasic sodium phosphate, sodium chloride, pH adjustment with NaOH and/or HCI, water.
>
> The reference fails to teach the specific elected second agent tyloxapol.
>
> Guy et al. teaches non-ionic surfactant surface active agent include polysorbate 80 and tyloxapol in 0.05-1%.
>
> It would have been obvious to one of ordinary skill in the art at the time of the invention 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. Hence, a skilled artisan would have had reasonable expectation of successfully producing a composition with similar efficacy and results.

Non-Final Office Action, p. 2-3.

The Examiner also rejected claims 49, 56, 60, and 64-68 under 35 U.S.C. § 103(a) as obvious over Yanni and Guy in further view of Gamache (WO 01/15677):

> Yanni et al. and Guy et al. do not teach the specific buffer boric acid and/or sodium borate/sodium tetraborate; thickners, polyvinylpyrrolidone; stabilizer is sodium sulfite.
>
> Gamache et al. teaches anti-inflammatory agents include bromfenac and Moxifloxacin, viscosity building agents include, for example, polyvinyl alcohol, polyvinyl pyrrolidone, methyl cellulose, hydroxypropyl methylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose, hydroxypropyl cellulose or other agents known to those skilled in the art. An appropriate buffer system (e. g., sodium phosphate, sodium acetate or sodium borate) may be added to prevent pH drift under storage conditions. Exemplified is an otic/nasal suspension: Ingredient 1B/1D agonist 0.1-1.0% w/v, Moxifloxacin 0.3% w/v, Benzalkonium Chloride 0.01% w/v, Edetate Disodium, USP 0.01% w/v, Sodium Chloride, USP 0.3% w/v, Sodium Sulfate, USP 1.2% w/v, Tyloxapol, USP 0.05% w/v, Hydroxyethylcellulose 0.25% w/v, Sulfuric Acid and/or Sodium Hydroxide, NF q. s., and purified water q. s. to 100%.
>
> It would have been obvious to one of ordinary skill in the art at the time of the invention to use the specific buffer boric acid and/or sodium borate/sodium tetraborate; thickners, polyvinylpyrrolidone; stabilizer is sodium sulfite. The motivation comes from the teaching of Gamache et al. that the anti-inflammatory agents, viscosity building agents, and buffer systems are interchangeable. Hence, a skilled artisan would have had reasonable expectation of successfully producing a composition with similar efficacy and results.

Id., p. 3-4.

The Examiner also maintained the provisional non-statutory rejection of claims 41-51, 53-56, 58-60, and 64-68 over copending application, Appl. Ser. No. 11/755,662.

xxii) Applicants' Response Dated September 6, 2011

On September 6, 2011, Applicants filed an Amendment that cancelled claims 42, 61, and 62, and amended claim 41:

> 41. (Currently Amended) An aqueous liquid preparation consisting essentially of the following two components, wherein the first component is 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and the second component is tyloxxapol ~~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 ammnium compound is included in said liquid preparation, the quaternary ammonium compound is ~~limited to~~ benzalkonium chloride.

In the remarks, Applicants referred to an interview with the Examiner that was held on September 1, 2011 and stated that the amendments were proposed by Applicants and suggested by the Examiner.

With respect to the obviousness rejection of claims 41-48, 50-51, 53-55, and 58-59 under 35 U.S.C. § 103(a) over Yanni and in view of Guy, Applicants stated that:

> As discussed during the interview, the rejection appears to take the position that Yanni discloses in Preparation XV a composition of bromfenac with polysorbate 80. However Preparation XV does not disclose bromfenac, the acid, but an amide derivative thereof.
>
> Moreover, Yanni teaches that bromfenac acids have problems such as difficulty in formulating stable solutions, and provoking ocular irritation. See column 1, line 60 to column 2, line 3. The object of Yanni is to make amide and ester derivatives of bromfenac which the inventors found to have better stability while having similar anti-inflammatory activity. See for example column 2, lines 23-43.
>
> Bromfenac is mentioned in Yanni in Table 1, merely as a reference compound for comparison purposes with the novel amide and ester derivatives of Yanni. It can be seen from the description of the anti-inflammatory tests described in columns 13 and 14 that bromfenac was tested merely in a 0.1% solution of the compound, and not in a pharmaceutical composition.
>
> The pharmaceutical compositions disclosed in the Tables of columns 16 and 17 of Yanni are directed to compositions of an "Active Agent" with polysorbate 80 and other components. The "Active Agent" is defined on lines 50-51 of column 16 to mean "one or more compounds of Formula I". The compounds of Formula I are described from the bottom of column 2 to 3. From the definition of "Y" in the compounds, it is apparent that these compounds are limited to the amide or ester of bromfenac and do not encompass the bromfenac acid itself.
>
> In summary, neither Preparation XV nor the remainder of Yanni disclose a composition of bromfenac as claimed, or its salt or hydrate, together with polysorbate 80 as contended in the rejection.
>
> Moreover, Yanni teach away from using bromfenac as claimed, due to problems with obtaining stable solutions and provoking ocular irritation. See column 1 line 60 to column 2 line 3.
>
> Therefore Yanni do not teach or suggest a composition of bromfenac with polysorbate 80.
>
> Guy is cited for teaching the equivalency of polysorbate 80 and tyloxapol.

However Guy is directed to solving the problem of agglomeration of water insoluble steroid compounds such as loteprednol etabonate. See for example column 2, lines 45-65. On the other hand, bromfenac is a nonsteroidal compound.

Therefore one 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.

According to the USTPO guidelines, "[i]t is improper to combine references where the references teach away from their combination." See MPEP § 2145, citing In re Grasselli, 713 F.2d 731, 743 (Fed. Cir. 1983); see also McGinley v. Franklin Sports, Inc., 262 F.3d 1339, 1354 (Fed.Cir. 2001) ("It is well-established that references which "teach away cannot serve to create a prima facie case of obviousness.") (citations omitted).

Moreover, the present inventors 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. Please see the description of Experimental Example 1 and Table 1 on pages 14-16 of the specification.

In the Experimental Example, the stability of an aqueous solution of bromfenac was measured by storing the bromfenac solution with polysorbate 80 (see Comparison Example 1) and, separately, with tyloxapol (see A-02), under conditions of pH 7.0 at 60°C for 4 weeks. The remaining rate % of bromfenac was measured after the test.

As shown in Table 1, only 51.3% of bromfenac remained in the aqueous solution when stored with polysorbate 80. In contrast, 73.8% of bromfenac remained in the aqueous solution when stored with tyloxapol.

Thus the present inventors have found that tyloxapol has an unexpected stabilizing effect on an aqueous solution of bromfenac in comparison to polysorbate 80. Therefore the present inventors have found that tyloxapol and polysorbate 80 are not equivalent compounds. Such unequivalency, and such remarkable effects, could not have been obvious to one skilled in the art from the cited references.

Response, 6-8.

With respect to the obviousness rejection of claims 49, 56, 60, and 54-68 under 35 U.S.C. § 103(a) over Yanni, Guy, and Gamache, Applicants stated that "the rejection of these claims is believed to be overcome in view of the foregoing amendments and remarks." *Id., p. 8.*

With respect to the provisional non-statutory double patenting rejection, the Applicants stated that all other grounds of rejection were believed to be overcome and respectfully requested withdrawal of the provisional rejection. *Id.*

xxiii) Final Office Action Mailed November 15, 2011

In a Final Office Action mailed on November 15, 2011, the Examiner maintained the rejection of claims 41-48, 50-51, 53-55, and 58-59 under 35 U.S.C. § 103(a) as obvious over Yanni in view of Guy and the rejection of claims 49, 56, 60, and 64-68 under 35 U.S.C. § 103(a) as obvious over Yanni and Guy in further view of Gamache. In response to Applicants' arguments, the Examiner stated that:

> Applicant's main argument is that "Bromfenac is mentioned in Yanni in Table 1, merely as a reference compound for comparison purposes with the novel amide and ester derivatives of Yanni. It can be seen from the description of the anti-inflammatory tests described in columns 13 and 14 that bromfenac was tested merely in a 0.1% solution of the compound, and not in a pharmaceutical composition." Examiner states Yanni clearly discloses a single topical dose of 0.1% drug solution/suspension comprising Bromfenac. The Examiners contention is that the reference does not specify the specific components of the comparative formulation (or in fact, the novel formulations) of the tests. However, the Example of the ophthalmic composition disclosing 0.01-0.5% of an active agent in a formulation renders obvious the use of the comparative example- Bromfenac, in such a formulation.

Final Office Action, p. 5-6.

The Examiner also maintained the provisional non-statutory rejection of claims 41, 43-51, 53-56, 58-60, and 64-68 over copending application, Appl. Ser. No. 11/755,662.

xxiv) Interview Summary Mailed November 15, 2011

In an Interview Summary mailed on November 15, 2011, the Examiner stated that an Interview with Applicants took place September 1, 2011 and that:

> Applicant argues – not necessarily is the claimed compound useful in the example
>
> Applicant will consider amending claims to Bromfenac and tyloxapol
>
> Applicant will delete the method claims.

Interview Summary.

xxv) Notice of Allowance and Examiner's Amendment mailed December 23, 2011

The Examiner issued the Notice of Allowance on December 23, 2011, allowing claims 41, 43-51, 53-56, 58-60, and 64-68 of the '006 Application. In the Notice, the Examiner provided an Examiner's Amendment which amend claims 41 and 64 with the addition of "wherein the hydrate is at least one selected from a ½ hydrate, 1 hydrate, and 3/2 hydrate" after the term "hydrate thereof". Authorization for the amendment was given in a telephone interview with Applicants on December 16, 2011. The Examiner also provided the reasons for allowance as follows:

> The composition as claimed are found to be patentable over the prior art because the prior art does not teach or fairly suggest an aqueous liquid preparation consisting essentially of the following two components, wherein the first component is 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof, and the second component is tyloxapol 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 benzalkonium chloride.
>
> The transitional phrase "consisting essentially of" limits the scope of a claim to the specified materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention. In re Herz, 537 F.2d 549, 551-52, 190 USPQ 461, 463 (CCPA 1976) (emphasis in original).
>
> The closest prior arts of record, namely Yanni et al. and Desai et al. Yanni et al. teaches a composition comprising an active agent see specifically Preparation XV (3-benzoylphenylacetic acid derivatives, salts are known) in 0.01-0.5%, polysorbate 80 in 0.01°/o, benzalkonium chloride, disodium EDTA, monobasic sodium phosphate, dibasic sodium phosphate, sodium chloride, pH adjustment with NaOH and/or HCl, water. 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 (column 3, lines 13-29, claims 4 and 7) and polysorbates such as tweens and tyloxapol and further comprising boric acid buffer (column 2, lines 18-44).
>
> 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 ofbromfenac in comparison with polysorbate 80.

> Please see the description of Experimental Example 1 and Table 1 on pages 14-16 of the specification. In the Experimental Example, the stability of an aqueous solution ofbromfenac was measured by storing the bromfenac solution with polysorbate 80 (see Comparison Example 1) and, separately, with tyloxapol (see A-02), under conditions of pH 7.0 at 60°C for 4 weeks. The remaining rate % of bromfenac was measured after the test. As shown in Table 1, only 51.3% ofbromfenac remained in the aqueous solution when stored with polysorbate 80. In contrast, 73.8% of bromfenac remained in the aqueous solution when stored with tyloxapol. Thus the present inventors have found that tyloxapol has an unexpected stabilizing effect on an aqueous solution ofbromfenac in comparison to polysorbate 80. Therefore the present inventors have found that tyloxapol and polysorbate 80 are not equivalent compounds. Such unequivalency, and such remarkable effects, could not have been obvious to one skilled in the art from the cited references. For the foregoing reasons, it is respectfully submitted that the teachings of the cited references do not suggest the claimed bromfenac preparation as amended, nor the unexpected properties of the preparation. Additionally, Desai et al. teach that the problems with benzalkonium chloride and other quaternary ammonium compounds can be avoided by using certain polymeric quaternary ammonium compounds in combination with boric acid. Hence, an essential component of the Desai composition is a polymeric quaternary ammonium compound. However, the instant claims as amended require that, when the claimed liquid preparation includes a quaternary ammonium compound, the quaternary ammonium compound is limited to benzalkonium chloride. Thus the polymeric quaternary ammonium compounds disclosed in Desai et al. are excluded from the amended claims.

Notice of Allowance, p. 42.

xxvi) Issuance of the '431 Patent on March 6, 2012

The '006 Application issued as U.S. Patent No. 8,129,431 with claims 1-22.

2. U.S. Patent No. 8,669,290

a) Priority Information and Related Applications

U.S. Patent No. 8,669,290 ("the '290 Patent") (Exhibit 4) issued March 11, 2014 from U.S. Application Serial No. 13/687,242 ("the '242 Application"), filed November 28, 2012, which is a division of U.S. Application Serial No. 13/353,653 ("the '653 Application"), filed January 19, 2012 and issued as U.S. Pat. No. 8,497,304; which is a division of U.S. Application Serial No. 10/525,006 ("the '006 Application"), which is a U.S. National Stage Application based on International Application PCT/JP2004/000350, filed on January 16, 2004, which claims priority to Japanese Application No. JP 2003-12427, filed January 21, 2003.

The '290 Patent contains thirty (30) claims. The named inventors are Shirou Sawa and Shuei Fujita, and the listed assignee on the face of the patent is Senju Pharmaceutical Co., Ltd. The '290 Patent is listed to expire on January 16, 2024.[6]

b) Claims of the '290 Patent

The thirty (30) claims of the '290 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; 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 %; and wherein the first component is a 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.01 to about 0.2 w/v %.

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

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

7. 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, and wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.02 w/v % to about 0.1 w/v %.

[6] The cited expiration date of the '290 Patent is based upon information available in the FDA Orange Book. *See* FDA Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations at http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm.

8. 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.

9. The aqueous liquid preparation according to claim 8, further comprising a quaternary ammonium salt.

10. The stable aqueous liquid preparation of claim 8, 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.

11. The aqueous liquid preparation according to claim 8, wherein the concentration of tyloxapol is from about 0.01 w/v % to about 0.05 w/v %; and wherein the first component is a 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.01 to about 0.2 w/v %.

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

13. The stable aqueous liquid preparation of claim 8, wherein the stable aqueous liquid preparation consists essentially of: (a) 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate; (b) tyloxapol; (c) boric acid; (d) sodium tetraborate; (e) EDTA sodium salt; (f) benzalkonium chloride; (g) polyvinylpyrrolidone; and (h) sodium sulfite; and wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.02 w/v % to about 0.1 w/v %.

14. 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; provided that the liquid preparation does not include mannitol.

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

16. The aqueous liquid preparation according to claim 14, wherein the first component is a 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt.

17. The aqueous liquid preparation according to claim 16, wherein the concentration of tyloxapol is from about 0.01 w/v % to about 0.05 w/v % and the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.05 to about 0.2 w/v %.

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

19. The stable aqueous liquid preparation of claim 14; 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 %.

20. The stable aqueous liquid preparation of claim 14, 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.

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

22. The stable aqueous liquid preparation of claim 20; 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.

23. The aqueous liquid preparation according to claim 20, wherein the concentration of tyloxapol is from about 0.01 w/v % to about 0.05 w/v %; and wherein the first component is a 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.01 to about 0.2 w/v %.

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

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

bromobenzoyl)phenylacetic acid sodium salt is from about 0.02 w/v % to about 0.1 w/v %.

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

27. The aqueous liquid preparation of claim 8, wherein the aqueous liquid preparation further satisfies the preservative efficacy standard of EP-criteria B of the European Pharmacopoeia as follows: viable cell counts of bacteria (*S. aureus, P. aeruginosa*) 24 hours and 7 days after inoculation decrease to not more than 1/10 and not more than 1/1000, respectively, and thereafter, the cell count levels off or decreases; and viable cell count of fungi (*C. albicans, A. niger*) 14 days after inoculation decreases to not more than 1/10, and thereafter, the cell count keeps the same level as that of 14 days after inoculation.

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

29. The aqueous liquid preparation of claim 20, wherein the aqueous liquid preparation further satisfies the preservative efficacy standard of EP-criteria B of the European Pharmacopoeia as follows: viable cell counts of bacteria (*S. aureus, P. aeruginosa*) 24 hours and 7 days after inoculation decrease to not more than 1/10 and not more than 1/1000, respectively, and thereafter, the cell count levels off or decreases; and viable cell count of fungi (*C. albicans, A. niger*) 14 days after inoculation decreases to not more than 1/10, and thereafter, the cell count keeps the same level as that of 14 days after inoculation.

30. The aqueous liquid preparation of claim 22, wherein the aqueous liquid preparation further satisfies the preservative efficacy standard of EP-criteria B of the European Pharmacopoeia as follows: viable cell counts of bacteria (*S. aureus, P. aeruginosa*) 24 hours and 7 days after inoculation decrease to not more than 1/10 and not more than 1/1000, respectively, and thereafter, the cell count levels off or decreases; and viable cell count of fungi (*C. albicans, A. niger*) 14 days after inoculation decreases to not more than 1/10, and thereafter, the cell count keeps the same level as that of 14 days after inoculation.

c) Specification of the '290 Patent

Because the '290 Patent claims priority to the '431 Patent as a divisional application, the '290 Patent contains the disclosure of the specification of the '431 Patent, which is also described above.

d) Prosecution History of the '290 Patent

The prosecution history of the '290 patent is attached as Exhibit 5. The application that led to the '290 Patent was filed as U.S. Application Serial No. 13/687,242 ("the '242 Application"), filed November 28, 2012, which is a division of U.S. Application Serial No. 13/353,653 ("the '653 Application"), filed January 19, 2012 and issued as U.S. Pat. No. 8,497,304; which is a division of U.S. Application Serial No. 10/525,006 ("the '006 Application"), which is a U.S. National Stage Application based on International Application PCT/JP2004/000350, filed on January 16, 2004, which claims priority to Japanese Application No. JP 2003-12427, filed January 21, 2003.

i) The '242 Application Claims as Filed and Track 1 Request

The '242 Application was filed on November 28, 2012 with original claims 1-18. Claims 1-18 are the same as originally filed claims 1-18 of the '006 Application, which is described *supra.* The '242 Application was filed with a Track 1 Request. This Request was granted by the PTO on January 14, 2013.

ii) Preliminary Amendment Dated November 28, 2012

In a Preliminary Amendment, Applicants cancelled claims 1-18 and submitted new claims 19-48:

> 19. (New) 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.
>
> 20. (New) The aqueous liquid preparation according to claim 19, further comprising a quaternary ammonium salt.
>
> 21. (New) The aqueous liquid preparation according to claim 19, wherein the first component is a 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt.
>
> 22. (New) The aqueous liquid preparation according to claim 19, wherein the concentration of tyloxapol is from about 0.01 w/v % to about 0.05 w/v %; and wherein the first component is a 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt, wherein the concentration of the 2-amino-3-(4-

bromobenzoyl)phenylacetic acid sodium salt is from about 0.01 to about 0.2 w/v %.

23. (New) The aqueous liquid preparation according to claim 22, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is about 0.1 w/v %.

24. (New) The aqueous liquid preparation according to claim 19, wherein the pH is from about 7.5 to about 8.5.

25. (New) The stable aqueous liquid preparation of claim 19, wherein the stable aqueous liquid preparation consists essentially of: (a) 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt, (d) sodium tetraborate, (e) EDTA sodium salt, (f) benzalkonium chloride, (g) polyvinylpyrrolidone, and (h) sodium sulfite, wherein said liquid preparation is formulated for ophthalmic administration, and wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.02 w/v % to about 0.1 w/v %.

26. (New) 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.

27. (New) The aqueous liquid preparation according to claim 26, further comprising a quaternary ammonium salt.

28. (New) The stable aqueous liquid preparation of claim 26, 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.

29. (New) The aqueous liquid preparation according to claim 26, wherein the concentration of tyloxapol is from about 0.01 w/v % to about 0.05 w/v %; and wherein the first component is a 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.01 to about 0.2 w/v %.

30. (New) The aqueous liquid preparation according to claim 29, wherein the pH is from about 7.5 to about 8.5.

31. (New) The stable aqueous liquid preparation of claim 26, wherein the stable aqueous liquid preparation consists essentially of: (a) 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate; (b) tyloxapol; (c) boric acid; (d) sodium tetraborate;

(e) EDTA sodium salt; (f) benzalkonium chloride; (g) polyvinylpyrrolidone; and (h) sodium sulfite; and wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.02 w/v % to about 0.1 w/v %.

32. (New) 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.

33. (New) The aqueous liquid preparation according to claim 32, further comprising a quaternary ammonium salt.

34. (New) The aqueous liquid preparation according to claim 32, wherein the first component is a 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt.

35. (New) The aqueous liquid preparation according to claim 34, wherein the concentration of tyloxapol is from about 0.01 w/v % to about 0.05 w/v % and the concentration of the 2-amino-3-(4-bromobenzoyl) phenylacetic acid sodium salt is from about 0.05 to about 0.2 w/v %.

36. (New) The aqueous liquid preparation according to claim 35, wherein the pH is from about 7.5 to about 8.5.

37. (New) The stable aqueous liquid preparation of claim 32; 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 %.

38. (New) The stable aqueous liquid preparation of claim 32, 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.

39. (New) The aqueous liquid preparation according to claim 38, further comprising a quaternary ammonium salt.

40. (New) The stable aqueous liquid preparation of claim 38; 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.

41. (New) The aqueous liquid preparation according to claim 38, wherein the concentration of tyloxapol is from about 0.01 w/v % to about 0.05 w/v %; and

wherein the first component is a 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.01 to about 0.2 w/v %.

42. (New) The aqueous liquid preparation according to claim 41, wherein the pH is from about 7.5 to about 8.5.

43. (New) The stable aqueous liquid preparation of claim 38, 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 0.02 w/v % to about 0.1 w/v %.

44. (New) The aqueous liquid preparation of claim 19, wherein the aqueous liquid preparation further satisfies the preservative efficacy standard of EP-criteria B of the European Pharmacopoeia.

45. (New) The aqueous liquid preparation of claim 26, wherein the aqueous liquid preparation further satisfies the preservative efficacy standard of EP-criteria B of the European Pharmacopoeia.

46. (New) The aqueous liquid preparation of claim 32, wherein the aqueous liquid preparation further satisfies the preservative efficacy standard of EP-criteria B of the European Pharmacopoeia.

47. (New) The aqueous liquid preparation of claim 38, wherein the aqueous liquid preparation further satisfies the preservative efficacy standard of EP-criteria B of the European Pharmacopoeia.

48. (New) The aqueous liquid preparation of claim 40, wherein the aqueous liquid preparation further satisfies the preservative efficacy standard of EP-criteria B of the European Pharmacopoeia.

In the Preliminary Amendment, Applicants remarked that claims 19-48 were patentable over prior art U.S. Patent No. 5,603,929 ("Desai"). Specifically, Applicants stated that:

> Desai does not disclose the currently claimed composition, with the ingredients combined as recited in the claims. Indeed, one skilled in the art would have interpreted Desai, at a time before applicant's invention, as disclosing a narrow and specific composition that differs significantly from that currently claimed by Applicant.
>
> Desai's objective is to provide a preservative system, the efficacy of which is not degraded or reduced in the presence of an acidic drug (such as diclofenac) that is incompatible with positively charged

preservatives. (Desai, column 1, lines 27-34, and column 2, lines 10-14.) Desai stated that its objective was achieved by combining a polymeric quaternary ammonium compound (also known as "polyquat") and boric acid. (Desai, column 2, lines 18-22.) The specification of the Desai patent presented preservative efficacy data for only one formulation (Formulation A). But in addition to a polyquat and boric acid, Formulation A also contained mannitol. (Desai, Example 1, column 4, lines 15-33.) During prosecution, Desai submitted a declaration providing comparative data to show that only the formulation having polyquat-1, though it also contained boric acid and mannitol, satisfied the preservative efficacy criteria, whereas formulations having benzalkonium chloride or benzothenium bromide did not. (Desai's Declaration dated 2/26/1996, Table 2, a copy of which is attached hereto) Desai made a statement regarding the role of mannitol in his compositions, contending it did not have any significant effect on preservative efficacy. (Desai's Supplemental Declaration, dated 7/2/1996, a copy of which is attached hereto) Those skilled in the art, however, would have had a much different understanding of Desai's disclosure and the role of mannitol prior to the time of the present invention.

That Desai's formulation satisfies the preservative efficacy was not due solely to polyquat-1 and boric acid, but to the combination of polyquat-1, boric acid, and mannitol. It had been known even before Desai that borate/polyol complexes worked as preservative systems. See, e.g., U.S. Patent No. 5,342,620 to Chowhan, cited by the examiner of the Desai's patent. Borate/polyol complexes enhance the preservative efficacy of a weak preservative, or a preservative amount, that otherwise would not satisfy the preservative efficacy standards. (Chowhan '620, column 1, line 67 to column 2, line 7.) Reading the Desai patent with the knowledge available in the art before Applicant's invention, the skilled artisan would have recognized that the borate/polyol complex, as a whole, contributed to increase the preservative efficacy of polyquat-1—not just boric acid.

Indeed, at the time Desai filed his application for patent, it was already known that mannitol acted to enhance the preservative efficacy of a weak preservative. For example, U.S. Patent No. 5,505,953 issued to Chowhan ("Chowhan '953") provided a comparison of the preservative efficacy of formulations with and without mannitol. (Chowhan '953, column 9, line 15 to column 10, line 26.) The formulations without mannitol failed to meet the British Pharmacopeia (1988) standards. (Chowhan '953, column 9, lines 44-48, and column 10, lines 21-25.) To the best of Applicant's knowledge, the preservative efficacy acceptance criteria of British Pharmacopeia and European Pharmacopeia are similar. Therefore, Chowhan '620 and Chowhan '953 showed that, without mannitol, Desai's objective of meeting the

preservative efficacy standard of both US Pharmacopeia XXII and European Phamiacopeia would not have been achieved.

Applicant has experimental results that corroborate what those skilled in the art already knew at the time of Desai and certainly before Applicant's invention: 1) that without mannitol, Desai's combination of only polyquat-1, at a concentration typically used in ophthalmic formulations, and boric acid does not satisfy preservative efficacy criteria, even for the US Phamiacopeia, and 2) that the Desai patent would have been interpreted as requiring the presence of mannitol in addition to boric acid to achieve the touted preservative efficacy.

In this regard, Applicant presents Tables 1 and 2. Table 1 provides the compositional details of six diclofenac formulations, some of which contain mannitol with polyquat-1 and boric acid, and some of which do not contain mannitol. Table 2 provides the preservative efficacy of the preservative in each foiniulation in Table 1.

In Table 1, DBP-1 corresponds closely to Desai's Formulations B and C. It also contains 3.5%w/v of mannitol, whereas Formulation B of Desai contains 1.6 %w/v of mannitol. The 0.005% w/v of polyquat-1 used in Desai's Formulations B and C, as well as in DBP-1, is a typical concentration for this preservative. Desai's Formulation A, on the other hand, has a much higher concentration-4% polyquat-1, a level not typically used in commercial ophthalmic products. Conducting the experiments, therefore, at 0.005% polyquat-1 more effectively shows the importance of mannitol in achieving Desai's stated purpose.

DBP-2 is the same as DBP-1, except it had a pH of 7.8 to discern any effect of pH.

DBP-3 and DBP-4 correspond to DBP-1 and DBP-2, respectively, without mannitol. The results for these foimulations show the requirement of mannitol in Desai's formuation.

DBP-5 and DBP-6 correspond to DBP-1 and DBP-2, respectively, without mannitol, but with tyloxapol. Tyloxapol is not a polyol but a polyether.

Table 1. Diclofenac/boric acid/polyol matrix

Ingredient	DBP-1 (%w/v)	DBP-2 (%w/v)	DBP-3 (%w/v)	DBP-4 (%w/v)	DBP-5 (%w/v)	DBP-6 (%w/v)
Sodium Diclofenac	0.1	0.1	0.1	0.1	0.1	0.1
HPMC (E4M)	0.1	0.1	0.1	0.1	0.1	0.1
Tromethamine	2.0	2.0	2.0	2.0	2.0	2.0
Boric Acid	1.2	1.2	1.2	1.2	1.2	1.2
Vitamin E TPGS	3.0	3.0	3.0	3.0	3.0	3.0
Mannitol	3.5	3.5	---	---	---	---
Polyquaternium-1	0.005	0.005	0.005	0.005	0.005	0.005
Tyloxapol	---	---	---	---	0.02	0.02
HCl/NaOH	pH to 7.4	pH to 7.8	pH to 7.4	pH to 7.8	pH to 7.4	pH to 7.8
Purified Water	qs to 100%	qs to 100%	qs to 100%	qs to 100%	qs to 100%	qs to 100%

Table 2 is a collection of tables presenting the preservative efficacy testing results for each of the foregoing formulations.

Table 2. Preservative Efficacy Testing Results

DBP-1: Diclofenac + Mannitol + PQ-1 pH 7.4

Organism	Time Intervals						
	0 hr	6 hr	24 hr	48 hr	7 day	14 day	28 day
A. brasiliensis	0.02	0.06	2.12	2.99	3.10	~3.79	~3.42
C. Albicans	1.01	2.99	>4.51	>4.51	>4.51	>4.51	>4.51
E. coli	2.65	>4.24	>4.24	>4.24	>4.24	>4.24	>4.24
S. aureus	~3.43	>4.49	>4.49	>4.49	>4.49	>4.49	>4.49
P. aeruginosa	>4.64	>4.64	>4.64	>4.64	>4.64	>4.64	>4.64

DBP-2: Diclofenac + Mannitol + PQ-1 pH 7.8

Organism	Time Intervals						
	0 hr	6 hr	24 hr	48 hr	7 day	14 day	28 day
A. brasiliensis	0.05	0.09	1.35	2.82	2.28	2.39	2.59
C. Albicans	0.83	3.06	>4.51	>4.51	>4.51	>4.51	>4.51
E. coli	3.06	>4.24	>4.24	>4.24	>4.24	>4.24	>4.24
S. aureus	~3.52	>4.49	>4.49	>4.49	>4.49	>4.49	>4.49
P. aeruginosa	>4.64	>4.64	>4.64	>4.64	>4.64	>4.64	>4.64

DBP-3: Diclofenac + PQ-1 pH 7.4 (No Mannitol)

Organism	Time Intervals						
	0 hr	6 hr	24 hr	48 hr	7 day	14 day	28 day
A. brasiliensis	0.03	0.34	2.01	~4.01	3.05	2.95	2.61
C. Albicans	~3.48	>4.51	>4.51	>4.51	>4.51	>4.51	>4.51
E. coli	~3.11	>4.24	>4.24	>4.24	>4.24	>4.24	>4.24
S. aureus	~3.37	>4.49	>4.49	>4.49	>4.49	>4.49	>4.49
P. aeruginosa	>4.64	>4.64	>4.64	>4.64	>4.64	>4.64	>4.64

DBP-4: Diclofenac + PQ-1 pH 7.8 (No Mannitol)

Organism	Time Intervals						
	0 hr	6 hr	24 hr	48 hr	7 day	14 day	28 day
A. brasiliensis	0.01	0.93	2.04	3.04	2.12	1.90	0.97
C. Albicans	>4.51	>4.51	>4.51	>4.51	>4.51	>4.51	>4.51
E. coli	~3.31	>4.24	>4.24	>4.24	>4.24	>4.24	>4.24
S. aureus	~3.79	>4.49	>4.49	>4.49	>4.49	>4.49	>4.49
P. aeruginosa	>4.64	>4.64	>4.64	>4.64	>4.64	>4.64	>4.64

DBP-5: Diclofenac + Tyloxapol + PQ-1 pH 7.4

Organism	Time Intervals						
	0 hr	6 hr	24 hr	48 hr	7 day	14 day	28 day
A. brasiliensis	0.06	1.19	2.21	2.96	3.06	2.93	1.08
C. Albicans	~3.32	>4.51	>4.51	>4.51	>4.51	>4.51	>4.51
E. coli	2.73	>4.24	>4.24	>4.24	>4.24	>4.24	>4.24
S. aureus	3.40	>4.49	>4.49	>4.49	>4.49	>4.49	>4.49
P. aeruginosa	~4.16	>4.64	>4.64	>4.64	>4.64	>4.64	>4.64

DBP-6: Diclofenac + Tyloxapol + PQ-1 pH 7.8

Organism	Time Intervals						
	0 hr	6 hr	24 hr	48 hr	7 day	14 day	28 day
A. brasiliensis	0.01	1.03	2.70	2.98	2.05	1.95	1.34
C. Albicans	>4.51	>4.51	>4.51	>4.51	>4.51	>4.51	>4.51
E. coli	~3.43	>4.24	>4.24	>4.24	>4.24	>4.24	>4.24
S. aureus	~3.69	>4.49	>4.49	>4.49	>4.49	>4.49	>4.49
P. aeruginosa	>4.64	>4.64	>4.64	>4.64	>4.64	>4.64	>4.64

The following Table 3 (from the Desai patent) shows the criteria needed to pass the preservative efficacy testing under US Pharmacopeia ("USP"), European Pharmacopeia A ("EP-A"), and European Pharmacopeia B ("EP-B"). EP-A has the most stringent criteria.

Table 3. Preservative Efficacy Acceptance Criteria

	Log Reduction of Organism Population		
Time Pull	USP	*Ph. Eur.* A (Target)	*Ph. Eur.* B (Min)
	For Bacteria:		
6 hours	—	2	—
24 hours	—	3	1
7 days	—	—	3
14 days	3	—	—
28 days	NI	NR	NI
	For Fungi:		
7 days	—	2	—
14 days	NI	—	1
28 days	NI	NI	NI

NR = No organisms recovered
NI = No increase at this or any following time pulls
— = No requirement at this time pull

In the results presented in Table 2, A. brasiliensis and C. Albicans are fungi, and *E. Coli*, *S. aureus*, and *P. Aeruginosa* are bacteria. The preservative efficacy against fungi, especially *A. brasiliensis*, is the most difficult to meet. If the preservative efficacy fails for any one microorganism, the formulation does not meet the preservation efficacy criteria.

Generally speaking, a lower pH of 7.4 is more effective than a pH of 7.8. However, whether a formulation meets the preservative efficacy criteria does not depend on pH in the range of 7.4-7.8.

> Only formulations containing all three ingredients, polyquat-1, boric acid, and mannitol (DBP-1 and DBP-2), meet all three preservative efficacy criteria required by Desai. None of the foimulations without mannitol (DBP-3 through DBP-6) satisfies any preservative efficacy because the population of the fungus *A. brasilensis* shows an increase from the previous time - point. As the tables show with regard to the USP and EP-B criteria, the population of *A. brasilensis* at 28 days is higher than at 14 days. Similarly, with respect to the EP-A criteria, the population of A. brasilensis at 28 days is higher than at 7 days.
>
> Thus, the data prove what the skilled person would have understood all along when reading the Desai patent: that, without mannitol, the fonnulations having polyquat-1 and boric acid do not achieve Desai's purpose of satisfying the preservative efficacy of USP XXII and European Pharmacopeia and that, to be operative for its intended purpose, Desai's formulations must contain mannitol.
>
> In view of the foregoing, Desai's formulations would not have rendered the claims of the present application obvious. The Desai formulations are different from those presently claimed, and there is no suggestion to avoid degradation of acidic drugs, such as bromfenac, by using tyloxapol.

Preliminary Amendment, p. 9-15 (emphasis in original).

iii) Restriction Requirement Mailed on March 25, 2013

In a Restriction Requirement mailed March 25, 2013, the Examiner required election of a species of "various quaternary ammonium salts." *Restriction Requirement, p. 2.*

iv) Applicants' Response Dated April 9, 2013

On April 9, 2013, the Applicants elected benzalkonium chloride as the species of quarternary ammonium salts and indicated that claims 19-48 read on the elected species.

v) Non-Final Office Action Mailed August 8, 2013

In a Non-final Office Action mailed on August 8, 2013, the Examiner rejected claims 44-48 under 35 U.S.C. § 112, second paragraph as indefinite. In particular, the Examiner stated that:

> Applicant has claimed the preservative efficacy standard is satisfied by EP-criteria B of the European Pharmacopoeia. Where possible, claims are to be complete in themselves. Incorporation by reference to a specific figure or table "is permitted only in exceptional circumstances where there is no practical way to define the invention in words and where it is more concise to incorporate by reference than duplicating a drawing or table into the claim. Incorporation by reference is a necessity doctrine, not for applicant's convenience." Ex parte Fressola,

27 USPQ2d 1608, 1609 (Bd. Pat. App. & Inter. 1993) (citations omitted).

Non-final Office Action, p. 2-3.

The Examiner also rejected claims 19, 21-24, 26, 28-30, 32, 34-36, 38, 40-42, and 44-48 under 35 U.S.C. § 103(a) as obvious over WO 01/15677 to Gamache et al. ("Gamache"). In particular, the Examiner stated:

> Gamache teaches compositions for otic and intranasal use (p.6, lines 5-6) that contain a combination of a 5-HT agonist and an anti-inflammatory agent (p. 6, lines 1-4; p. 12 lines 9-10) or alternatively sequential or concurrent dosing of separate compositions that contain the 5-HT antagonist in one composition and the anti-inflammatory agent in a second composition (p. 12, lines 9-11); specifically claimed is the anti-inflammatory specie bromfenac (2-amino-3-(4-bromobenzoyl)phenylacetic acid). 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; p. 13, lines 6-8); aqueous formulations are preferred (p. 10, lines 11-14); tyloxapol is taught in a concentration of 0.05 % (w/v) (p. 16, line 30). The salt form of bromfenac in solution will be the same when the acid is dissolved in a solution followed by adjustment to the desired pH with NaOH/HCl (Gamache, p. 15, line 33) as when the sodium salt is dissolved in solution adjusted to the same pH; in this case Gamache also teaches the sodium salt limitation of instant claim 21. The concentration range of 0.01-1.0% overlaps and encompasses the claimed concentration range of the sodium salt of bromfenac instantly claimed.
>
> Although, the reference does not exemplify an aqueous liquid preparation comprising the first component and second component, it would have been obvious for one of ordinary skill in the art at the time of the invention to select concentrations of bromfenac in the invention of Gamache. It would have been obvious to adjust the concentration of tyloxapol, to see what the effect would be on the solubility and stability of the aqueous preparations, which would have resulted in the effective concentrations of the instant claims. 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, in a more aqueous soluble ionic form. The motivation would have been to prepare pharmaceutical products with optimal drug dosage and stability. Hence, a skilled artisan would have reasonable expectation of successfully producing an efficacious and stable drug.

Id., p. 4-5.

The Examiner also rejected claims 24, 31, 37, and 43 under 35 U.S.C. § 103(a) as obvious over Gamache in view of Desai. In particular, the Examiner stated:

> Gamache, et al. fails to teach quaternary ammonium salt[.]
>
> Desai et al. teaches a composition comprising 0.05% Bromfenac, 0.05% Disodium EDTA, and 0.01% Benzalkonium chloride.
>
> It would have been obvious to one of ordinary skill in the art to incorporate benzalkonium chloride into the ophthalmic formulation. The motivation comes from the teaching that benzalkonium chloride acts as a preservative in ophthalmic formulation. Hence, a skilled artisan would have had reasonable expectation of successfully producing similar efficacy and results.

Id., p. 5-6.

The Examiner also rejected claims 24, 31, 37, and 43 under 35 U.S.C. § 103(a) as obvious over Gamache in view of U.S. Patent No. 4,910,225 to Ogawa et al. ("Ogawa") and U.S. Patent No. 6,162,393 to De Bruiju et al. ("De Bruiju"). In particular, the Examiner stated:

> Gamache, et al. fails to teach sodium tetraborate, sodium sulfite, and polyvinylpyrrolidone, boric acid.
>
> Ogawa et al. teaches sodium sulfite and polyvinyl pyrrolidone increased the stability of an eye drop formulation remarkably. 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.
>
> De Bruiju et al. various buffer systems such as citrate, phosphate (appropriate mixtures of Na.sub.2 HPO.sub.4, NaH.sub.2 PO.sub.4, and KH.sub.2 PO.sub.4), borate (boric acid, sodium tetraborate) potassium metaborate and mixtures), bicarbonate, and tromethamine and other appropriate nitrogen-containing buffers (such as ACES, BES, BICINE, BIS-Tris, BIS-Tris Propane, HEPES, HEPPS, imidazole, MES, MOPS, PIPES, TAPS, TES, Tricine) can be used to ensure a physiologic pH between about pH 6.5 and 8.5 in an eye solution.
>
> It would have been obvious to one of ordinary skill in the art to incorporate sodium tetraborate, sodium sulfite, and polyvinylpyrrolidone, boric acid into the ophthalmic formulation. The motivation comes from the teaching that sodium sulfite and polyvinyl pyrrolidone increased the stability of an eye drop formulation and further that various buffer systems such as citrate, phosphate

> (appropriate mixtures of Na.sub.2 HPO.sub.4, NaH.sub.2 PO.sub.4, and KH.sub.2 PO.sub.4), borate (boric acid, sodium tetraborate) potassium metaborate and mixtures), bicarbonate, and tromethamine and other appropriate nitrogen-containing buffers (such as ACES, BES, BICINE, BIS-Tris, BIS-Tris Propane, HEPES, HEPPS, imidazole, MES, MOPS, PIPES, TAPS, TES, Tricine) can be used to ensure a physiologic pH between about pH 6.5 and 8.5 in an eye solution. Hence, a skilled artisan would have had reasonable expectation of successfully producing similar efficacy and results.

Id., p. 6-7.

Claims 19, 21-24, 26, 28-30, 32, 34-36, 38, 40-42, and 44-48 were rejected as non-statutory obvioussness-type double patenting over claims 1-8 of U.S. Patent No. 7,829,544. The Examiner stated that:

> Although the claims at issue are not identical, they are not patentably distinct from each other because the claims in the patent are drawn to an aqueous solution preparation comprising (a) an aminoglycoside antibiotic or its pharmacologically acceptable salt, (b) bromfenac or its pharmacologically acceptable salt and (c) nicotinamide whereas the claims herein are drawn to 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.

Id., p. 7-8.

Claims 19, 21-24, 26, 28-30, 32, 34-36, 38, 40-42, and 44-48 were also rejected as non-statutory obvioussness-type double patenting over claims 1-22 of U.S. Patent No. 8,129,431. The Examiner stated that:

> Although the claims at issue are not identical, they are not patentably distinct from each other because the claims in the patent are drawn to an aqueous liquid preparation consisting essentially of the following two components, wherein the first component is 2-amino-3-(4-bromobenzoyl)phenylaceticacid 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 the second component is tyloxapol 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 benzalkonium chloride whereas the claims herein are drawn to 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 ½ 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.

Id., p. 8-9.

Claims 19, 21-24, 26, 28-30, 32, 34-36, 38, 40-42, and 44-48 were also provisionally rejected as non-statutory obvioussness-type double patenting over pending claims 1-5 of copending U.S. Appl. Ser. No. 11/755,662. The Examiner stated that:

> Although the claims at issue are not identical, they are not patentably distinct from each other because the claims in the copending application are drawn to a method of treating pain and/or inflammation associated with an ocular disease, injury or disorder comprising administering to a patient, in need of such treatment, a stabilized aqueous liquid solution comprising 2-amino-3-(4-bromobenzoyl) phenylacetic acid or a pharmaceutically acceptable salt thereof or a hydrate thereof at a concentration ranging from 0.05% to 0.1% administered once or twice a day, or at a concentration ranging from 0.12% to 0.24% administered once a day, and an alkyl aryl polyether alcohol type polymer whereas the claims herein are drawn to 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.

Id., p. 9.

Claims 19, 21-24, 26, 28-30, 32, 34-36, 38, 40-42, and 44-48 were also provisionally rejected as non-statutory obvioussness-type double patenting over pending claims 1-5 of copending U.S. Appl. Ser. No. 13/353,653. The Examiner stated that:

> Although the claims at issue are not identical, they are not patentably distinct from each other because the claims in the copending application are drawn to an aqueous liquid preparation comprising 2-amino-3-(4- bromobenzoyl)phenylacetic acid sodium salt thereof or a

hydrate thereof, and polyoxyl 40 stearate, wherein the concentration of the 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% whereas the claims herein are drawn to 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.

Id., p. 10.

vi) Applicants' Response and Terminal Disclaimers Submitted October 22, 2013

In a response dated October 22, 2013, Applicants amended claims 19, 25, 27, 32, and 44-48:

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.

25. (Currently amended) The stable aqueous liquid preparation of claim 19, 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, and wherein the concentration of the 2amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.02 w/v% to about 0.1 w/v%.

27. (Currently amended) The aqueous liquid preparation according to claim 26, further comprising a quaternary ammonium salt, and wherein the first component is the sole pharmaceutical active ingredient contained in the preparation.

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.

44. (Currently amended) The aqueous liquid preparation of claim 19, wherein the aqueous liquid preparation further satisfies the preservative efficacy standard of EP-criteria B of the European Pharmacopoeia as follows:

viable cell counts of bacteria (8. aureus, P.aeruginosa) 24 hours and 7 days after inoculation decrease to not more than 1/1aand not more than 1/1 000, 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 1/1 0, and thereafter,

the cell count keeps the same level as that of 14 days after inoculation.

45. (Currently amended) The aqueous liquid preparation of claim 26, wherein the aqueous liquid preparation further satisfies the preservative efficacy standard of EP-criteria B of the European Pharmacopoeia as follows:

viable cell counts of bacteria (8. aureus, P.aeruginosa) 24 hours and 7 days after inoculation decrease to not more than 1/1aand not more than 1/1 000, 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 1/1 0, and thereafter,

the cell count keeps the same level as that of 14 days after inoculation.

46. (Currently amended) The aqueous liquid preparation of claim 32, wherein the aqueous liquid preparation further satisfies the preservative efficacy standard of EP-criteria B of the European Pharmacopoeia as follows:

viable cell counts of bacteria (8. aureus, P.aeruginosa) 24 hours and 7 days after inoculation decrease to not more than 1/1aand not more than 1/1 000, 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 1/1 0, and thereafter,

the cell count keeps the same level as that of 14 days after inoculation.

47. (Currently amended) The aqueous liquid preparation of claim 38, wherein the aqueous liquid preparation further satisfies the preservative efficacy standard of EP-criteria B of the European Pharmacopoeia as follows:

viable cell counts of bacteria (8. aureus, P.aeruginosa) 24 hours and 7 days after inoculation decrease to not more than 1/1aand not more than 1/1 000, 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 1/1 0, and thereafter,

the cell count keeps the same level as that of 14 days after inoculation.

48. (Currently amended) The aqueous liquid preparation of claim 40, wherein the aqueous liquid preparation further satisfies the preservative efficacy standard of EP-criteria B of the European Pharmacopoeia as follows:

viable cell counts of bacteria (8. aureus, P.aeruginosa) 24 hours and 7 days after inoculation decrease to not more than 1/1aand not more than 1/1 000, 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 1/1 0, and thereafter,

the cell count keeps the same level as that of 14 days after inoculation.

In response to the rejection of claims 44-48 under 35 U.S.C. § 112, second paragraph as indefinite, Applicants stated that the rejection was "deemed to be overcome by the foregoing amendments". *Response, p. 10.*

With respect to the rejection of claims 19, 21-24, 32, 34-36, 38, 40-42, 44, and 46-48 under 35 U.S.C. § 103(a) as obvious over Gamache, Applicants stated that:

> Claims 19, 27 and 32 now recite that the preparation comprises the first component, 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof (i.e. "bromfenac"), as the sole pharmaceutical active ingredient contained in the preparation.
>
> 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. Gamache's compositions may contain additional pharmaceutical active ingredients.
>
> Gamache does not teach or suggest any composition comprising bromfenac as the sole pharmaceutical active ingredient.
>
> Thus, Gamache does not teach or suggest claims 19, 27 or 32 as amended. Accordingly, Gamache fails to teach or suggest claims 21-24, 34-36, 38, 40-42, 44 and 46-48 which are dependent upon claims 19 and 32.
>
> Consequently, Gamache does not render these claims obvious.

B. Claims 26, 28-30 and 45

Claim 26 recites that "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."

Gamache does not teach or suggest any preparation comprising bromfenac and tyloxapol, wherein greater than 90% of the original amount of bromfenac remains after storage at 60 °C for 4 weeks.

Gamache disclosed generally that anti-inflammatory drugs, such as bromfenac or others, may be used in a composition including any surfactants "known to those skilled in the art," including polysorbate 80. However, 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 Serial No. 10/525,006.

Applicant recognized this problem and surprisingly found that the degradation of bromfenac could be avoided by specifically including tyloxapol in the preparation.

Thus, the preparation of claim 26, and its dependent claims, are not obvious from Gamache.

Id., p. 11-12.

With respect to the rejection of claims 20, 27, 33, and 39 under 35 U.S.C. § 103(a) as obvious over Gamache in view of Desai, Applicants stated that:

> Claim 20 is dependent upon independent claim 19. As pointed out above, claim 19 is nonobvious over Gamache because Gamache does not teach or suggest any composition wherein bromefenac is the sole pharmaceutical active ingredient. Therefore, adding Desai to show the use of benzalkonium chloride still does not overcome the deficiency of Gamache. Therefore, claim 20 is nonobvious over Gamache in view of Desai.
>
> Claim 27 is amended to recite that bromfenac is the sole pharmaceutical active ingredient in the preparation. As pointed out above, claim 27 is nonobvious over Gamache because Gamache does not teach or suggest any composition wherein bromefenac is the sole pharmaceutical active ingredient. Therefore, adding Desai to show the use of benzalkonium chloride still does not overcome the deficiency of

> Gamache. Therefore, claim 27 is nonobvious over Gamache in view of Desai.
>
> Claims 33 and 39 are dependent upon independent claim 32. As pointed out above, claim 32 is nonobvious over Gamache because Gamache does not teach or suggest any composition wherein bromfenac is the sole pharmaceutical active ingredient. Therefore, adding Desai to show the use of benzalkonium chloride still does not overcome the deficiency of Gamache. Moreover, all Desai's experiments include mannitol, which is excluded from the compositions of present claims 33 and 39. Therefore, the combination of Gamache and Desai does not teach or suggest any composition wherein bromfenac is the sole pharmaceutical active ingredient and wherein mannitol is excluded. Consequently, claims 33 and 39 are nonobvious over Gamache in view of Desai.

Id., p. 12.

With respect to the rejection of claims 25, 31, 37, and 43 under 35 U.S.C. § 103(a) as obvious over Gamache in view of Ogawa and De Bruiju, Applicants stated that:

> Claim 25 is dependent upon independent claim 19. As pointed out above, claim 19 is nonobvious over Gamache because Gamache does not teach or suggest any composition wherein bromefenac is the sole pharmaceutical active ingredient. Therefore, adding Ogawa and De Bruiju to show the use of sodium tetraborate, sodium sulfite, polyvinylpyrrolidone and boric acid does not overcome the deficiency of Gamache. Therefore, claim 25 is nonobvious over Gamache in view of Ogawa and De Bruiju.
>
> Claim 31 is dependent upon independent claim 26. As pointed out above, claim 26 is nonobvious over Gamache because Gamache does not teach or suggest any preparation comprising bromfenac and tyloxapol, wherein greater than 90% of the original amount of bromfenac remains after storage at 60 °C for 4 weeks. Therefore, adding Ogawa and De Bruiju to show the use of sodium tetraborate, sodium sulfite, polyvinylpyrrolidone and boric acid does not overcome the deficiency of Gamache. Therefore, claim 31 is nonobvious over Gamache in view of Ogawa and De Bruiju.
>
> Claim 37 is dependent upon independent claim 32. As pointed out above, claim 32 is nonobvious over Gamache because Gamache does not teach or suggest any composition wherein bromefenac is the sole pharmaceutical active ingredient. Therefore, adding Ogawa and De Bruiju to show the use of sodium tetraborate, sodium sulfite, polyvinylpyrrolidone and boric acid does not overcome the deficiency

> of Gamache. Therefore, claim 37 is nonobvious over Gamache in view of Ogawa and De Bruiju.
>
> Claim 43 is dependent upon independent claim 32. As pointed out above, claim 32 is nonobvious over Gamache because Gamache does not teach or suggest any composition wherein bromefenac is the sole pharmaceutical active ingredient. Therefore, adding Ogawa and De Bruiju to show the use of sodium tetraborate, sodium sulfite, polyvinylpyrrolidone and boric acid does not overcome the deficiency of Gamache. Therefore, claim 43 is nonobvious over Gamache in view of Ogawa and De Bruiju.

Id., p. 13.

With respect to the nonstatutory double patenting rejections over U.S. Patent Nos. 7,829,544 and 8,129,431 and U.S. Ser. No. 13/353,653, Applicants submitted a Terminal Disclaimer. With respect to the provisional nonstatutory double patenting rejection over U.S. Ser. No. 11/755,662, Applicants noted that the '662 application was expressed abandoned previously.

vii) Interview Summary Mailed January 15, 2014

In an Interview Summary mailed on January 15, 2014, the Examiner stated that an Interview with Applicants took place January 8, 2014 and that:

> In the interest of compact prosecution, a proposal was made to the Applicant to overcome the remaining issues and proceed to allowance. In the interest of compact prosecution, a proposal was made to the Applicant to overcome the remaining issues and proceed to allowance. Applicant agreed and gave the Examiner authorization to make the appropriate claim amendments in an Examiner's Amendment.

Interview Summary.

viii) Notice of Allowance and Examiner's Amendment mailed January 15, 2014

The Examiner issued the Notice of Allowance on January 15, 2014, which allowed claims 19-48. In the Notice, the Examiner provided an Examiner's Amendment which amended claim 26 to insert "the first component is the sole pharmceutical active ingreident contained in the preparation" after the term "hydrate" and claim 27 to delete ", and wherein the first component is the sole pharmceutical active ingreident contained in the preparation" after the term "salt." In the Notice, the Examiner provided the reasons for allowance as follows:

> The composition as claimed are found to be patentable over the prior art because the prior art does not teach or fairly suggest 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 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.

The closest prior arts of record, namely Chen et al. (US 6383471), teach a pharmaceutical composition including a hydrophobic therapeutic agent having at least one ionizable functional group, and a carrier. The carrier includes an ionizing agent capable of ionizing the functional group, a surfactant, and optionally solubilizers, triglycerides, and neutralizing agents (abstract). The reference teaches a hydrophobic therapeutic agent to include bromfenac (2-amino-3-(4-bromobenzoyl)phenalyacetic acid)(see claim 4). The hydrophobic therapeutic agent is used in less than about 1°/0 by weight, and typically less than about 0.1% or 0.01% by weight (see col 4 lines 58-60) (renders obvious the limitation of claims 8 and 24). The reference further teaches surfactants inclusive of polyethylene glycol fatty acid esters and additionally teaches polyethylene glycol fatty acid monoesters such as peg-15 stearate, etc (see claims 21-22 24 and 27). The surfactants are selected from the group consisting of alcohols; polyoxyethylene alkylethers; fatty acids; glycerol fatty acid esters; acetylated glycerol fatty acid esters; lower alcohol fatty acids esters; polyethylene glycol fatty acids esters; polyethylene glycol glycerol fatty acid esters; polypropylene glycol fatty acid esters; polyoxyethylene glycerides; lactic acid derivatives of mono/diglycerides; propylene glycol diglycerides; sorbitan fatty acid esters; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene-polyoxypropylene block copolymers; transesterified vegetable oils; sterols; sterol derivatives; sugar esters; sugar ethers; sucroglycerides; polyoxyethylene vegetable oils; and polyoxyethylene hydrogenated vegetable oils. The pharmaceutical compositions of the present invention can be provided in the form of a solution preconcentrate; i.e., a composition as described above, and intended to be dispersed with water, either prior to administration, in the form of a drink, or dispersed in vivo (col 34 lines 63-68) (reads on an aqueous liquid preparation). The reference also teaches preservatives (see claim 64). Although formulations specifically suited to oral administration are presently preferred, the compositions of the present invention can also be formulated for topical, transdermal, ocular, pulmonary, vaginal, rectal, transmucosal or parenteral administration (col 35 lines 9-20). Chen et al. further teaches components that can be incorporated into the composition include inorganic acids inclusive of boric acid (col 46, line 6), solubilizer such as polyvinylpyrrolidone (claim 49),

exemplifications of carriers comprising Edetate Disodium (col 4 table 20 formulations 65 and 66), and ionizing agents that deprotonate the acidic functional groups of the therapeutic agent are pharmaceutically acceptable organic or inorganic bases, inclusive of sodium hydroxide (col 11 lines 12-13) (reads on the limitations of claim 22).

However, Applicant presents excellent effects are clearly demonstrated by Experiments 1 to 3 of the present specification. Experiment 1 -- Stability of sodium 2-amino-3-(4-bromobenzoyl)phenyl acetate was evaluated. Namely, two eye drops of sodium 2-amino-3-(4-bromobenzoyl) phenylacetate comprising the components as shown in Table 1 were prepared, filled respectively into a polypropylene container and subjected to a stability test at 60°C for 4 weeks. As is apparent from Table 1, the stability test was carried out under the conditions of pH 7.0 at 60°C for 4 weeks. Table 1 clearly shows that sodium 2-amino-3- (4-bromobenzoyl)phenylacetate in polyoxyl 40 stearate-containing preparation was more stable than that in polysorbate 80- containing preparation. As is apparent from Table 2, the remaining rate of sodium 2-amino-3-(4-bromobenzoyl)phenylacetate in the compositions A-07 and A-08 containing 0.02 w/v and 0.05 w/v % of polyoxyl 40 stearate is not less than 90 % after storage at 60°C for 4 weeks. Table 2 clearly shows that the compositions containing 0.02 w/v % and 0.05 w/v of polyoxyl 40 stearate have sufficient stability for eye drops. The arguments are persuasive.

The composition as claimed are found to be patentable over the prior art because the prior art does not teach or fairly suggest 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 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.

Notice, p. 4-6.

C. INVALIDITY OF THE ORANGE BOOK LISTED PATENTS

1. Invalidity of the '431 Patent

As explained in detail below, prior to the 102(b) date of the '431 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.

For at least the reasons below, the manufacture, use, offer to sell, or sale of Innopharma's proposed Bromfenac Sodium product, which is the subject of ANDA No. 206-326, will not infringe any valid and enforceable claim of the '431 Patent.

2. Invalidity Analysis of the '431 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.

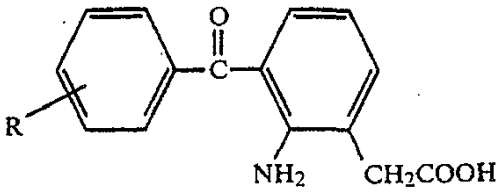
For at least the following reasons set forth below, claims 1-22 of the '431 Patent are obvious under 35 U.S.C. § 103 over the prior art described herein.

3. The Scope and Content of the Prior Art

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

U.S. Patent No. 4,910,225 ("the '225 patent") (Exhibit 6) was published on March 20, 1990, which is more than one year prior to the earliest filing date available to the'431 patent. Accordingly, the '225 patent is available as prior art under 35 U.S.C. § 102(b).

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	To make 100 ml
pH 8	

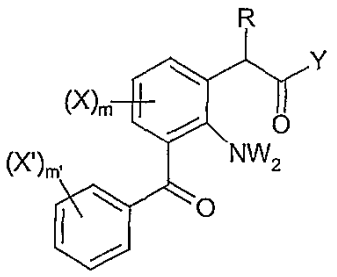
Id., Example 6. In the above Example 6, sodium 3-(4-bromobenzoyl)-2-aminophenyl-acetate monohydrate refers to the monohydrate of the sodium salt of bromfenac.

[redacted]

b) WO 02/13804 to Kapin et al.

WO 02/13804 ("the '804 publication") (Exhibit 7) was published on February 21, 2002, which is prior to the earliest filing date available to the '431 Patent. Additionally, the '804 publication was published more than one year prior to the effective U.S. filing date of the '431 Patent. Accordingly, the '804 publication is available as prior art under 35 U.S.C. § 102(b).

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.

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

U.S. Patent No. 5,414,011 ("the '011 patent") (Exhibit 8) was published on May 9, 1995, which is more than one year prior to the earliest filing date available to the '431 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 '431 Patent.

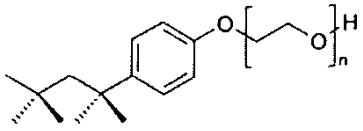
The '011 patent teaches stable, clear, antimicrobially effective ophthalmic formulations which included an NSAID, and a preservative system formed of a quaternary ammonium preservative and a nonionic polyoxyethylated octylphenol surfactant, all in an aqueous vehicle. *'011 patent, Abstract.* "The preservative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

The preservative system 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 Number	**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, poly-oxyethyleneoxystearic acid triglyceride, polyethylene glycol

The preferred nonionic surfactants including 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:



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.

d) WO 00/57887 to Shull et al.

WO 00/57887 ("the '887 publication") (Exhibit 9) was published on October 5, 2000, which is prior to the earliest priority date of the '431 Patent. Therefore, the '887 publication qualifies as prior art under 35 U.S.C. § 102(a) (pre-AIA). The '887 publication also qualifies as prior art under 35 U.S.C. § 102(e) (pre-AIA) as of its filing date of March 31, 1999 as Serial No. 09/282,847. The '887 publication was disclosed to the PTO during prosecution of the '431 patent.

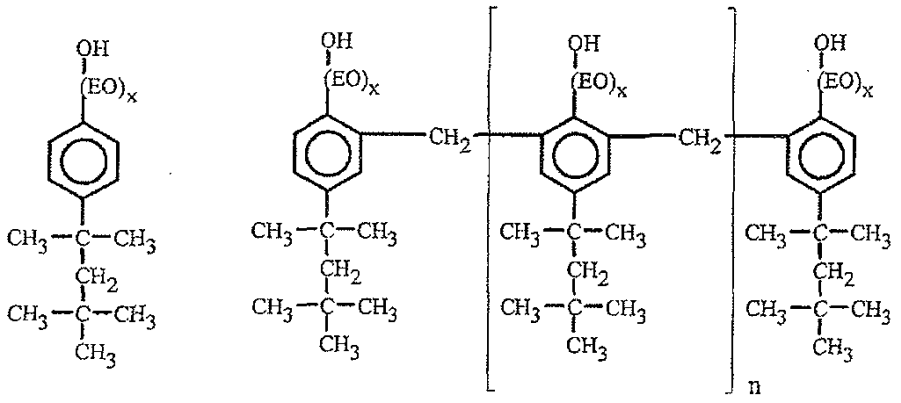
The '887 publication teaches that *p*-boronophenylalanine (p-BPA), water, carbohydrate or polyol, and base may be mixed to produce a basic solution of p-boronophenylalanine and the carbohydrate. *'887 publication*, page 10. The pH is adjusted to between 7.3 and 7.5 to produce a salt-free solution of the p-BPA-carbohydrate or p-BPA-polyol complex. *Id.* Freeze-drying the solution gives a salt-free p-BPA complex as a white solid. *Id.* The carbohydrate or polyol may be fructose (*'887 publication*, Example 1), sorbitol (*'887 publication*, Example 6), or mannitol (*'887 publication*, Example 7). The *p*-BPA complexes can be stored for a long time. *Id.*, page 4.

The '887 publication further teaches that p-boronophenylalanine "has a solubility of 1.6 g/L in water, which is insufficient for medical uses." *'887 publication*, page 2. Complexation with a monosaccharide or a reduced sugar increases solubility. The carbohydrate or polyol may be fructose (*'887 publication*, Example 1), sorbitol (*'887 publication*, Example 6), or mannitol (*'887 publication*, Example 7). A freeze-dried complex of sodium L-p-boronophenylalanine-D-fructose is a solid which can be hydrated with warm water (60°C, solubility approximately 0.1 g/mL [100 g/L]), and which "remains completely dissolved after prolonged standing (i.e., 48 hrs) at room temperature." *Id.*, Example 1.

e) 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 '431 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 '431 Patent.

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.[7] 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.*

f) 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 '431 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 '431 Patent.

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

[7] Alauddin et al. "Effect of Organic Additives on the Cloud Point of Triton X-100 Micelles." *Journal of Applied Sciences, 9:2301-06 (2009) (Exhibit 16).*

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.

g) U.S. Patent No. 2,454,541 to Bock et al.

U.S. Patent No. 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 '431 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 '431 Patent.

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.

h) U.S. Patent No. 6,107,343 to Sallmann et al.

U.S. Patent No 6,107,343 ("the '343 patent") (Exhibit 13) was published on August 22, 2000, which is more than one year prior to the earliest filing date available to the '431 Patent. Accordingly, the '343 patent is available as prior art under 35 U.S.C. § 102(b).

The '343 patent describes ophthalmic compositions with diclofenac potassium. With respect to solubilizers used for the described ophthalmic compositions, the '343 patent discloses that tyloxapol is a preferred solubilizer:

> The solubilizers used for an ophthalmic composition of the present invention are, for example, tyloxapol, fatty acid glycerol poly-lower alkylene glycol esters, fatty acid poly-lower alkylene glycol esters, polyethylene glycols, glycerol ethers or mixtures of those compounds. A specific example of an especially preferred solubilizer is a reaction product of castor oil and ethylene oxide, for example the commercial products Cremophor EL® or Cremophor RH 40 ®. Reaction products of castor oil and ethylene oxide have proved to be particularly good solubilizers that are tolerated extremely well by the eye. Another preferred solubilizer is tyloxapol.

'343 patent, col. 4, ll. 53-62.

The '343 patent describes a specific example (Example 2) of an aqueous preparation comprising diclofenac benzalkonium chloride and the non-ionic surfactant, tyloxapol:

EXAMPLE 2

Formulation of diclofenac potassium eye drops (0.05%)

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

Id., col. 8, ll. 1-15.

i) U.S. Patent No. 6,274,609 to Yasueda et al.

U.S. Patent No. 6,274,609 ("the '609 patent") (Exhibit 14) was published on August 14, 2001, which is more than one year prior to the earliest filing date available to the '431 Patent. Accordingly, the '609 patent is available as prior art under 35 U.S.C. § 102(b).

The '609 patent describes pranlukasut compositions with various solubilizing agents:

TABLE 4

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

TABLE 4-continued

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

*polyoxyethylene hydrogenated castor oil 60
**butylated hydroxytoluene

'609 Patent, col. 6, l. 65 – col. 7, l. 19.

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

TABLE 5

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

Id., col. 7, ll. 25-34.

As shown in Table 5, solutions with tyloxapol (A and B) had the greatest residual rate.

j) Hara, Yoshiyuki, Clinics & Drug Therapy 2002, 19:1014-1015

Hara, Yoshiyuki, "Bromfenac sodium hydrate," *Clinics & Drug Therapy 2002, 19:1014-1015* ("Hara") (Exhibit 15) was published in 2002, which is more than one year prior to the earliest filing date available to the '431 Patent. Accordingly, Yuan is available as prior art under 35 U.S.C. § 102(b).

Hara describes "[b]romfenac sodium hydrate [as] a type of NSAID that was developed in order to address the needs of clinical sites, and it is indicated for use in a broad range of

[ophthalmic] conditions, from inflammation of the outer ocular area to post-operative inflammation of the anterior ocular segment." *Hara*, 1014:1:2. Hara compared bromfenac with three other NSAIDs that existed in the prior art—pranoprofen, indomethacin, and diclofenac sodium. *Hara*, 1014:2:2-1014:2:5. Hara concluded that bromfenac "shows superior efficacy in treating anterior eye inflammation and post-operative inflammation." *Hara*, 1015:2:2.

Specifically, Hara explains that bromfenac "is indicated for use in a broad range of conditions, from inflammation of the outer ocular area to post-operative inflammation of the anterior ocular segment" *Hara*, 1014:1:2, but states that "the range of application [of diclofenac] is limited." *Hara*, 1014:2:5-1015:1:1.

k) Differences between the Prior Art and the Claims of the '431 Patent

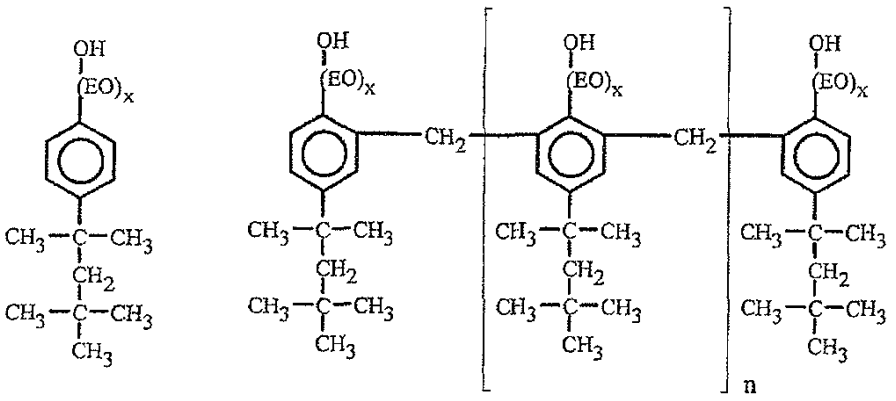
i) Independent Claim 1 of the '431 Patent is obvious under 35 U.S.C. § 103 over the '225 Patent in view of the '804 Publication, the '011 Patent, and Regev

Claim 1 recites an aqueous liquid preparation consisting essentially of 2-amino-3-(4-bromobenzoyl)phenylacetic acid (bromfenac); and tyloxapol. Bromfenac is further characterized as being present in the form of the free acid, a pharmacologically acceptable salt thereof, or a hydrate thereof. 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, may contain the quaternary ammonium compound benzalkonium chloride.

The specification defines tyloxapol as an alkyl aryl polyether alcohol type polymer. *'431 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 additionally contain one or more additives selected from the group consisting of a buffer, thickener, stabilizer, chelating agent, and pH controlling agent. *Id., claim 7.* The buffer may be boric acid and/or sodium borate; the thickener may be polyvinylpyrrolidone; the stabilizer may be sodium sulfite; the chelating agent may be sodium edetate; and the pH controlling agent may be sodium hydroxide. *Id., claim 8.*

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

x = 9-10

Tyloxapol

x = 8-10 n < 6

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

Claim 1 contains the transitional phrase "consisting 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 '431 Patent, the language "consisting essentially of" was introduced to define over prior art reciting 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 '431 Patent (Exhibit 3), Response dated March 26, 2008.

Accordingly, claim 1 requires an aqueous liquid preparation consisting essentially of bromfenac; tyloxapol; optionally benzalkonium chloride; and optionally various biologically inactive additives. Claim 1 excludes active ingredients other than bromfenac.

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

EXAMPLE 6

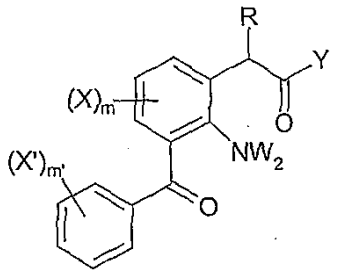
Ophthalmic Solution

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 consisting essentially of the monohydrate of the sodium salt of bromfenac; polysorbate 80; benzalkonium chloride; and various biologically inactive additives. Example 6 does not include active ingredients other than bromfenac. The only difference between Example 6 of the '225 patent and claim 1 of the '431 Patent is the nonionic surfactant, i.e. polysorbate 80 rather than tyloxapol. The '431 Patent asserts that the use of tyloxapol instead of polysorbate 80 surprisingly and significantly improves the stability of the formulation.

However, before the filing of the '431 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 '431 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, as the sole active ingredient; tyloxapol; and benzalkonium chloride. *Id.*, Formulation 3 on page 7. Formulation 3 has the following constituents:

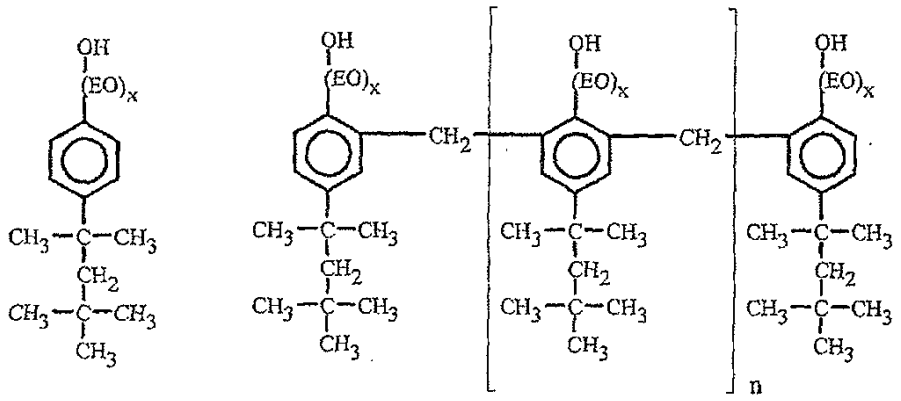
Formulation 3

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%

Thus, the '804 publication teaches the substitutability of tyloxapol for polysorbate 80 as a surfactant for aqueous ophthalmic solutions, including bromfenac generically.

It was therefore known at the time of filing the '431 Patent, 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." *Id.*, 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." *'011 patent*, 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 in the art 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 '431 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).



Triton X-100 Tyloxapol

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

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

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.[8] 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 in the art 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 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 in the art 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

[8] Alauddin et al. "Effect of Organic Additives on the Cloud Point of Triton X-100 Micelles." *Journal of Applied Sciences, 9: 2301-2306 (2009) (Exhibit 16).*

combination of the prior art teaches all of the elements of claim 1, and claim 1 is *prima facie* obvious over the prior art.

ii) Independent Claim 1 of the '431 Patent is obvious under 35 U.S.C. § 103 over the '225 Patent in view of the '804 Publication, the '011 Patent, Yuan, and the '541 patent

As discussed *supra*, the formulation of Example 6 of the '225 patent differs from the formulation of claim 1 in that it contains the nonionic surfactant polysorbate 80 rather than the nonionic surfactant tyloxapol.

Also 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.

Also as discussed above, 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 in the art 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 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.

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, the combination of the prior art teaches all of the elements of claim 1, and claim 1 is *prima facie* obvious over the prior art.

iii) Independent Claim 1 of the '431 Patent is obvious under 35 U.S.C. § 103 over the '225 Patent in view of the '343 Patent and the '609 Patent, or alternatively, over the '343 Patent in view of the '225 Patent and Hara

As discussed *supra*, the formulation of Example 6 of the '225 patent differs from the formulation of claim 1 in that it contains the nonionic surfactant polysorbate 80 rather than the nonionic surfactant tyloxapol.

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

EXAMPLE 2

Formulation of diclofenac potassium eye drops (0.05%)

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

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

A person of ordinary skill in the art would have had reason to combine the '225 and '343 patents to arrive at the formulation recited in claim 1 as it was known prior to the '431 Patent that acidic NSAIDs (such as bromfenac) containing an ionizable carboxylic acid group form complexes with quaternary ammonium preservatives, such as BAC in ophthalmic formulations. The interaction of the NSAID with BAC results in complexes that were known to precipitate out of the ophthalmic formulation, which is problematic because it (1) renders the preservative (e.g., BAC) less available to serve its function and (2) reduces the availability of the NSAID (e.g., bromfenac).

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

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

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

TABLE 4

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

TABLE 4-continued

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

*polyoxyethylene hydrogenated castor oil 60
**butylated hydroxytoluene

TABLE 5

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

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

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

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

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

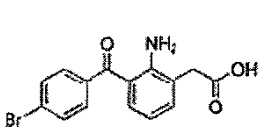
function it had been known to perform' and yields no more than one would expect from such an arrangement, the combination is obvious." *KSR*, 550 U.S. at 416 (citing *Sakraida v. AG Pro, Inc.*, 425 U.S. 273 (1976)).

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

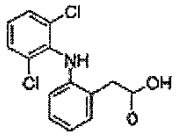
As an alternative to switching nonionic surfactants in the aqueous ophthalmic preparations of the '225 and '343 patents, it would have also been obvious to switch NSAIDs. Thus, it would have been obvious to use bromfenac from the '225 patent's Example 6 instead of diclofenac in the '343 patent's Example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

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

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



Bromfenac



Diclofenac

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

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

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

A person of ordinary skill in the art would have known that substituting bromfenac for diclofenac would have yielded predictable results because both are NSAIDs with similar pharmacological properties. Furthermore, a person of ordinary skill in the art facing a design need to formulate a stable bromfenac solution would have found it at least obvious to try to prepare an aqueous liquid bromfenac preparation comprising tyloxapol because Hara teaches that there were only four NSAID ophthalmic drugs available on the market by 2003, "resulting in limited choices." Hara, 1014:2:2. Therefore, in view of the '343 and '225 patents, and in further view of Hara, a person of ordinary skill would have reasonably expected to be able to make and use an aqueous liquid ophthalmic preparation within the scope of claim 1 of the '431 patent and accordingly, claim 1 is invalid.

iv) Dependent Claim 2 of the '431 Patent is obvious under 35 U.S.C. § 103, over (A) the '225 Patent in view of the '804 Publication, the '011 Patent, and Regev or alternatively, (B) the '225 Patent in view of the '804 Publication, the '011 Patent, Yuan, and the '541 patent, or alternatively, (C) the '225 Patent in view the '343 Patent and the '609 Patent, or alternatively, (D) the '343 Patent in view of the '225 Patent and Hara

Claim 2 depends from claim 1, and further limits claim 1 by reciting that the first component in the composition of claim 1 is a 2-amino-3-(4-bromobenzoyl)phenylacetic acid (bromfenac) sodium salt.

Example 6 of the '225 patent describes an aqueous liquid preparation containing a sodium salt of bromfenac, specifically the monohydrate of the sodium salt of bromfenac, as required by claim 2. *'225 patent*, Example 6.

Accordingly, claim 2 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. In the alternative, claim 2 is invalid under 35 U.S.C. § 103(a) as obvious over the '225 patent in view of the '804 publication, the '011 patent, Yuan, and the '541 patent. In another alternative, claim 2 is invalid under 35 U.S.C. § 103(a) as obvious over the '225 patent in view the '343 patent and the '609 patent. In a further alternative, claim 2 is invalid under 35 U.S.C. § 103(a) as obvious over the '343 patent in view of the '225 patent and Hara.

[redacted]

v) *Dependent Claims 3-5 and 11 of the '431 Patent are obvious under 35 U.S.C. § 103 over (A) the '225 Patent in view of the '804 Publication, the '011 Patent, and Regev or alternatively, (B) the '225 Patent in view of the '804 Publication, the '011 Patent, Yuan, and the '541 patent, or alternatively, (C) the '225 Patent in view the '343 Patent and the '609 Patent, or alternatively, (D) the '343 Patent in view of the '225 Patent and Hara*

Claim 3 depends from claim 1, and further limits claim 1 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 0.5 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 0.5 w/v %.

Claim 4 depends from claim 3, and further limits claim 3 by reciting that the concentration of tyloxapol is from about 0.01 w/v % to about 0.3 w/v % and the concentration of the bromfenac sodium salt is from about 0.05 to about 0.2 w/v %.

Claim 5 depends from claim 4, and further limits claim 4 by reciting that the concentration of the bromfenac sodium salt is about 0.1 w/v %.

Claim 11 depends from claim 4, and further limits claim 4 by reciting that the concentration of the bromfenac sodium salt is about 0.2 w/v %.

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 3-5 and 11. *'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 3-5. *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. The tyloxapol and polysorbate 80 are used in the same concentration. *Id.*, Formulations 1-3. Accordingly, the '804 publication teaches that tyloxapol may be substituted for polysorbate 80 at the same concentration. 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 0.15 w/v% of tyloxapol, as encompassed by claims 3-5.

In the alternative, the '343 patent describes an ophthalmic formulation containing diclofenac (an acidic NSAID), BAC, and tyloxapol with express disclosure tyloxapol concentrations of 1.0 mg/ml and 0.1 mg/ml, *i.e.*, 1 and 0.1 w/v%, in Examples 2 and 3 respectively. Thus, the '343 patent's disclosure of 0.1 w/v% of tyloxapol is a species within the genus of claimed tyloxapol ranges of claims 3 and dependent claims.

Accordingly, claims 3-5 and 11 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. Alternatively, claims 3-5 and 11 are invalid under 35 U.S.C. § 103(a) as obvious over the '225 patent in view of the '804 publication, the '011 patent, Yuan, and the '541 patent. In another alternative, claims 3-5 and 11 are invalid under 35 U.S.C. § 103(a) as obvious over the '225 patent in view the '343 patent and the '609 patent. In a further alternative, claims 3-5 and 11 are invalid under 35 U.S.C. § 103(a) as obvious over the '343 patent in view of the '225 patent and Hara.

vi) Dependent Claims 6, 12 and 15 of the '431 Patent are obvious under 35 U.S.C. § 103 over (A) the '225 Patent in view of the '804 Publication, the '011 Patent, and Regev or alternatively, (B) the '225 Patent in view of the '804 Publication, the '011 Patent, Yuan, and the '541 patent, or alternatively, (C) the '225 Patent in view the '343 Patent and the '609 Patent, or alternatively, (D) the '343 Patent in view of the '225 Patent and Hara

Claim 6 depends from claim 4, and further limits claim 4 by reciting that the concentration of the tyloxapol is about 0.02 w/v %.

Claim 12 depends from claim 4, and further limits claim 4 by reciting that the concentration of the tyloxapol is about 0.3 w/v %.

Claim 15 depends from claim 11, and further limits claim 11 by reciting that the concentration of the tyloxapol is about 0.02 w/v %.

With regard to claims 6 and 15, the '804 publication shows that surfactants may be used in formulations of 3-benzoylphenylacetic acids at a concentration of 0.01% w/v. *Id.* The '804 publication shows ophthalmic formulations of 3-benzoylphenylacetic acids and their derivatives containing polysorbate 80 at a concentration of 0.01 w/v%; and tyloxapol at a concentration of 0.01 w/v%. *Id.*, Formulations 1-3. In view of the '804 publication, 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 with 0.01 w/v% of tyloxapol. This differs from the value recited in claims 6 and 15 by a factor of 2.

Furthermore, the '011 patent teaches NSAID solutions containing BAC and 0.02 w/v% octoxynol 40. As discussed above, Regev or Yuan and the '541 patent would have motivated a person of ordinary skill in the art to replace the octoxynol with tyloxapol.

With regard to claim 12, Example 6 of the '225 patent teaches an aqueous liquid preparation containing polysorbate 80 in a concentration of 0.15 g/100 ml (0.15 w/v%). *'225 patent, Example 6.* The '804 publication teaches that tyloxapol may be substituted for polysorbate 80 without changing concentration. 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 0.15 w/v% polysorbate 80 with 0.15 w/v% of tyloxapol. This differs from the value recited in claim 12 by a factor of 2. The '225 patent additionally teaches that an aqueous liquid preparation may contain polysorbate 80 in a concentration of 0.3 g/100 ml (0.3 w/v%), as recited in claim 12. *'225 patent, Col. 7, Experimental Example 3.*

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

The '431 Patent reports that a solution of sodium 2-amino-3-(4-bromobenzoyl)phenylacetate (bromfenac sodium) and BAC in an eye drop is less stable in the presence of a tyloxapol surfactant at a concentration of 0.15g/100 ml (0.15 w/v%) than in the presence of a tyloxapol surfactant at a concentration of 0.02g/100 ml (0.02 w/v%). *'431 Patent*, Table 1; col. 7, ll. 57-64. However, there is no evidence that there is any difference in stability in the presence of a tyloxapol surfactant at a concentration of 0.02 w/v%, compared to a tyloxapol surfactant at a concentration of concentration of 0.01g/100 ml. Similarly, there is no evidence that there is any difference in stability in the presence of a tyloxapol surfactant at a concentration of 0.3 w/v%, compared to a tyloxapol surfactant at a concentration of concentration of 0.15g/100 ml. Accordingly, the Patentee has failed to show that:

a) a tyloxapol concentration of 0.02 w/v% is critical, compared to the prior art concentration of 0.01 w/v%; or

b) a tyloxapol concentration of 0.3 w/v% is critical, compared to the prior art concentration of 0.15 to 0.3 w/v%.

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

Accordingly it would have been obvious to a person of ordinary skill in the art to optimize the concentration of tyloxapol provided in the '804 publication. Therefore claims 6, 12, 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. Alternatively, claims 6, 12, 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, Yuan, and the '541 patent. In another alternative, claims 6, 12, and 15 are invalid under 35 U.S.C. § 103(a) as obvious over the '225 patent in view the '343 patent and the '609 patent. In a further alternative, claims 6, 12, and 15 are invalid under 35 U.S.C. § 103(a) as obvious over the '343 patent in view of the '225 patent and Hara.

vii) Dependent Claims 7, 8, 13, 14, 16 and 17 of the '431 Patent are obvious under 35 U.S.C. § 103 over (A) the '225 Patent in view of the '804 Publication, the '011 Patent, and Regev or alternatively, (B) the '225 Patent in view of the '804 Publication, the '011 Patent, Yuan, and the '541 patent, or alternatively, (C) the '225 Patent in view the '343 Patent and the '609 Patent, or alternatively, (D) the '343 Patent in view of the '225 Patent and Hara

Claim 7 depends from claim 1, and further limits claim 1 by reciting that the aqueous liquid preparation of claim 1 further includes one or more additives selected from the group consisting of a preservative, buffer, thickener, stabilizer, chelating agent, and pH controlling agent.

Claim 8 depends from claim 7, and further limits claim 7 by reciting that the preservative is benzalkonium chloride; the buffer is boric acid and/or sodium borate; the thickener is polyvinylpyrrolidone; the stabilizer is sodium sulfite; the chelating agent is sodium edetate (EDTA); and the pH controlling agent is sodium hydroxide.

Claim 13 depends from claim 12, and further limits claim 12 by reciting that the concentration of the aqueous liquid preparation of claim 1 further includes one or more additives selected from the group consisting of a preservative, buffer, thickener, stabilizer, chelating agent, and pH controlling agent.

Claim 14 depends from claim 13, and further limits claim 13 by reciting that the preservative is benzalkonium chloride; the buffer is boric acid and/or sodium borate; the thickener is polyvinylpyrrolidone; the stabilizer is sodium sulfite; the chelating agent is sodium edetate (EDTA); and the pH controlling agent is sodium hydroxide.

Claim 16 depends from claim 15, and further limits claim 15 by reciting that the aqueous liquid preparation of claim 15 further includes one or more additives selected from the group consisting of a preservative, buffer, thickener, stabilizer, chelating agent, and pH controlling agent.

Claim 17 depends from claim 16, and further limits claim 16 by reciting that the preservative is benzalkonium chloride; the buffer is boric acid and/or sodium borate; the thickener is polyvinylpyrrolidone; the stabilizer is sodium sulfite; the chelating agent is sodium edetate (EDTA); and the pH controlling agent is sodium hydroxide.

The formulation of Example 6 of the '225 patent has a defined pH, and additionally contains boric acid and/or sodium borate, as recited in claims 8, 14, and 17 and encompassed by claims 7, 13, and 16; polyvinylpyrrolidone, as recited in claims 8, 14, and 17 and encompassed by claims 7, 13, and 16; sodium sulfite, as recited in claims 8, 14, and 17 and encompassed by claims 7, 13, and 16; and a sodium salt of EDTA, as recited in claims 8, 14, and 17 and encompassed by claims 7, 13, and 16. *Id.*, Example 6. "The pH adjustment is generally conducted with sodium hydroxide or hydrochloric acid, for instance..." *Id.*, col. 3, ll. 62-64.

The '343 patent further suggests that it would have been desirable to use a solution containing: (i) the preservative BAC to inhibit microbial growth, (ii) the buffer borate to prevent pH changes, (iii) the thickener PVP to act as a carrier, (iv) the stabilizer sodium hydrogen sulfite to prevent oxidation reactions, (v) the chelating agent disodium edetate, and (vi) the pH controlling agents hydrochloric acid and sodium hydroxide to set a suitable pH for an aqueous liquid preparation for ophthalmic administration. *'343 patent*, col. 8, ll. 1-15, col. 4, ll. 23-30, col. 5, ll. 8-10, col. 5, ll. 47-53, col. 10, ll. 22, and col. 14, l. 14.

Since the identical excipients are taught in the prior art, claims 7–8, 13–14, and 16–17 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. Alternatively, claims 7–8, 13–14, and 16–17 are invalid under 35 U.S.C. § 103(a) as obvious over the '225 patent in view of the '804 publication, the '011 patent, Yuan, and the '541 patent. In another alternative, claims 7–8, 13–14, and 16–17 are invalid under 35 U.S.C. § 103(a) as obvious over the '225 patent in view the '343 patent and the '609 patent. In a further alternative, claims 7–8, 13–14, and 16–17 are invalid under 35 U.S.C. § 103(a) as obvious over the '343 patent in view of the '225 patent and Hara.

viii) Dependent Claims 9 and 10 of the '431 Patent are obvious under 35 U.S.C. § 103 over (A) the '225 Patent in view of the '804 Publication, the '011 Patent, and Regev or alternatively, (B) the '225 Patent in view of the '804 Publication, the '011 Patent, Yuan, and the '541 patent, or alternatively, (C) the '225 Patent in view the '343 Patent and the '609 Patent, or alternatively, (D) the '343 Patent in view of the '225 Patent and Hara

Claim 9 depends from claim 8, and further limits claim 8 by reciting that the pH of the aqueous liquid preparation of claim 8 is from about 7 to about 9.

Claim 10 depends from claim 8, and further limits claim 8 by reciting that the pH of the aqueous liquid preparation of claim 8 is from about 7.5 to about 8.5.

The formulation of Example 6 of the '225 patent has a pH of 8, as encompassed by claims 9 and 10. *'225 patent*, Example 6.

In addtion, Hara expressly discloses a pH of 8.0-8.6 which is encompassed by claims 9 and 10. *Hara,* 1015:1:2.

Accordingly, claims 9 and 10 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. Alternatively, claims 9 and 10 are invalid under 35 U.S.C. § 103(a) as obvious over the '225 patent in view of the '804 publication, the '011 patent, Yuan, and the '541 patent. In another alternative, claims 9 and 10 are invalid under 35 U.S.C. § 103(a) as obvious over the '225 patent in view the '343 patent and the '609 patent. In a further alternative, claims 9 and 10 are invalid under 35 U.S.C. § 103(a) as obvious over the '343 patent in view of the '225 patent and Hara.

ix) Independent Claim 18 of the '431 Patent is obvious under 35 U.S.C. § 103 over the '225 Patent in view of the '804 Publication, the '011 Patent, and Regev or, alternatively, in view of the '804 Publication, the '011 Patent, Yuan, and the '541 patent

Claim 18 recites an aqueous liquid preparation consisting essentially of 2-amino-3-(4-bromobenzoyl)phenylacetic acid (*i.e.*, bromfenac); tyloxapol; boric acid; sodium tetraborate; EDTA sodium salt; benzalkonium chloride; polyvinyl pyrrolidone; and sodium sulfite. Bromfenac is further characterized as being present in the form of the free acid, a pharmacologically acceptable salt thereof, or a hydrate thereof. 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, and contains benzalkonium chloride as the only quaternary ammonium compound in the formulation.

Claim 18 contains the transitional phrase "consisting 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 '431 Patent, the language "consisting essentially of" was introduced to define over prior art reciting 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 '431 Patent, Response dated March 26, 2008.

Accordingly, claim 18 requires an aqueous liquid preparation consisting essentially of bromfenac; tyloxapol; boric acid; sodium tetraborate (borax); EDTA sodium salt (edetate sodium salt); benzalkonium chloride; polyvinylpyrrolidone; and sodium sulfite. Claim 18 excludes active ingredients other than bromfenac.

Claim 18 is very similar to clam 1, except that it recites a specific list of excipients. These are all shown by the '225 patent, the only difference being the use of polysorbate instead of tyloxapol, as shown in the table below:

Claim 18 of the '431 patent	**Example 6 of the '225 patent**
Bromfenac hydrates	Bromfenac monohydrate

Claim 18 of the '431 patent	Example 6 of the '225 patent
Tyloxapol	Polysorbate 80
Boric acid	Boric acid
Sodium tetraborate	Borax
EDTA sodium salt	Disodium edetate
Benzalkonium chloride	Benzalkonium chloride
Polyvinylpyrrolidone	Polyvinylpyrrolidone
Sodium sulfate	Sodium sulfite

As discussed in detail above with regard to claim 1, a person of ordinary skill in the art would have been motivated to replace polysorbate 80 as described in the '225 patent, specifically to improve the stability of the formulation. For example, the '804 publication describes topical formulations comprising a 3-benzoylphenylacetic acid or a derivative thereof (*e.g.*, bromfenac) 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. By describing these formulation, the '804 publication suggests that tyloxapol may be substituted for polysorbate 80.

It was known at the time of filing the '431 Patent, that a nonionic surfactant was important for stabilizing an aqueous solution of an NSAID and benzalkonium chloride. For example, the '011 patent teaches that a non-steroidal anti-inflammatory drug (NSAID) is "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." *'011 patent*, col. 2, ll. 48-53. 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." *Id.*, col. 2, line 66-col. 3, line 4. "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 in the art 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 octoxynol polyoxyethylated octylphenol surfactants and Tyloxapol were also known prior to the filing of the '431 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). However, tyloxapol has a higher cloud point and lower critical micelle concentration than Triton X-100. 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 in the art 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 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 in the art 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 of the prior art teaches all of the elements of claim 18, and claim 18 would have been *prima facie* obvious over the prior art.

In the alternative, Yuan explains that quaternary ammonium compounds, such as CTAB, and polyoxyethylated octylphenol surfactants, such as Triton X-100, form mixed micelles thereby providing the improved stability of NSAIDs combined with quaternary ammonium preservatives.

Moreover, the '541 patent teaches that ethoxylated phenol-formaldehyde surfactants, e.g., tyloxapol, are stable and are not dissociated as are the micelles of conventional surfactants under adverse conditions, such as changes in concentration or temperature.

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, form stable micelles under similar adverse conditions.

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, the combination of the prior art teaches all of the elements of claim 18, and claim 18 would have been *prima facie* obvious over the prior art.

x) *Independent Claim 18 of the '431 Patent is obvious under 35 U.S.C. § 103 over the '225 Patent in view of the '343 Patent and the '609 Patent, or alternatively, over the '343 Patent in view of the '225 Patent and Hara*

As discussed *supra*, the formulation of Example 6 of the '225 patent differs from the formulation of claim 18 in that it contains the nonionic surfactant polysorbate 80 rather than the nonionic surfactant tyloxapol.

Also discussed above, the '343 patent describes a specific example (Example 2) of an aqueous preparation comprising diclofenac benzalkonium chloride and the non-ionic surfactant, tyloxapol. *'343 Patent,* col. 8, ll. 1-15. The '343 patent, therefore, provides the missing non-ionic surfactant tyloxapol in an aqueous liquid opthalmic formulation of another NSAID (diclofenac potassium).

In addition it was also known that tyloxapol was a preferred or better solubilizer than polysorbate 80 for acidic compounds in aqueous ophthalmic formulations. The '343 patent teaches that tyloxapol is a preferred solubilizer. *'343 patent*, col. 4, l. 62. The '609 patent further provides motivation to use tyloxapol over polysorbate. According to the '609 patent, solutions with tyloxapol (A and B) had the greatest residual rate of pranlukasut while solutions with polysorbate 80 (D-E) had lower residual rates. *'609 Patent*, col. 6, l. 65 – col. 7, l. 34.

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

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

Since a person of ordinary skill in the art would have been motivated in view of the '343 and '609 patents, to replace polysorbate 80 with tyloxapol, the combination of the prior art teaches all of the elements of claim 18, and claim 18 is *prima facie* obvious over the prior art.

In an alternative, Hara describes bromfenac as superior to diclofenac and provides a person of ordinary skill in the art a reason to substitute the diclofenac in the '343 patent's Example 2 with the bromfenac in the '225 patent's Example 6.

Hara describes "[b]romfenac sodium hydrate [as] a type of NSAID that was developed in order to address the needs of clinical sites, and it is indicated for use in a broad range of [ophthalmic] conditions, from inflammation of the outer ocular area to post-operative

[redacted]

inflammation of the anterior ocular segment." *Hara*, 1014:1:2. Hara compared bromfenac with three other NSAIDs that existed in the prior art—pranoprofen, indomethacin, and diclofenac sodium. *Hara*, 1014:2:2-1014:2:5. Hara concluded that bromfenac "shows superior efficacy in treating anterior eye inflammation and post-operative inflammation." *Hara*, 1015:2:2.

A person of ordinary skill in the art, familiar with the '343 and '225 patents, would have had a reason to combine their teachings because the '343 patent teaches an aqueous liquid ophthalmic formulation of diclofenac formulated with tyloxapol and benzalkonium chloride, and Hara teaches that bromfenac [sodium hydrate] as disclosed in the '225 patent, is broadly applicable for treatment of various ophthalmic conditions, and preferable as compared to diclofenac. Thus, a person of ordinary skill in the art, reading '343 and '225 patents, would have had a reason to substitute the bromfenac of '225 patent's Example 6 for diclofenac in '343 patent's Example 2.

A person of ordinary skill in the art would have known that substituting bromfenac for diclofenac would have yielded predictable results because both are NSAIDs with similar pharmacological properties. Furthermore, a person of ordinary skill in the art facing a design need to formulate a stable bromfenac solution would have found it at least obvious to try to prepare an aqueous liquid bromfenac preparation comprising tyloxapol because Hara teaches that there were only four NSAID ophthalmic drugs available on the market by 2003, "resulting in limited choices." Hara, 1014:2:2. Therefore, in view of the '343 and '225 patents and in further view of Hara, a person of ordinary skill in the art would have reasonably expected to be able to make and use an aqueous liquid ophthalmic preparation within the scope of claim 18 of the '431 patent and accordingly, claim 18 is invalid.

xi) Dependent Claim 19 of the '431 Patent is obvious under 35 U.S.C. § 103 over (A) the '225 Patent in view of the '804 Publication, the '011 Patent, and Regev or alternatively, (B) the '225 Patent in view of the '804 Publication, the '011 Patent, Yuan, and the '541 patent, or alternatively, (C) the '225 Patent in view the '343 Patent and the '609 Patent, or alternatively, (D) the '343 Patent in view of the '225 Patent and Hara

Claim 19 depends from claim 18, and further limits claim 18 by reciting that the composition of claim 18 contains bromfenac in the form of a bromfenac sodium salt.

Example 6 of the '225 patent describes an aqueous liquid preparation containing a sodium salt of bromfenac, specifically the monohydrate of the sodium salt of bromfenac, as required by claim 19. *'225 patent*, Example 6.

Accordingly, 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. Alternatively, 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, Yuan, and the '541 patent. In another alternative, claim 19 is invalid under 35 U.S.C. § 103(a) as obvious over the '225 patent in view the '343 patent and the '609 patent. In a

further alternative, claim 19 is invalid under 35 U.S.C. § 103(a) as obvious over the '343 patent in view of the '225 patent and Hara.

xii) Dependent Claim 20 of the '431 Patent is obvious under 35 U.S.C. § 103 over (A) the '225 Patent in view of the '804 Publication, the '011 Patent, and Regev or alternatively, (B) the '225 Patent in view of the '804 Publication, the '011 Patent, Yuan, and the '541 patent, or alternatively, (C) the '225 Patent in view the '343 Patent and the '609 Patent, or alternatively, (D) the '343 Patent in view of the '225 Patent and Hara

Claim 20 depends from claim 19, and further limits claim 19 by reciting that:

the concentration of the bromfenac sodium salt is froJm about 0.01 to about 0.5 w/v %; and

the concentration of the tyloxapol is about 0.02 w/v %.

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 claim 20. *'225 patent*, 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 shows ophthalmic formulations of 3-benzoylphenylacetic acids and their derivatives containing polysorbate 80 at a concentration of 0.01 w/v%; and tyloxapol at a concentration of 0.01 w/v%. *Id.* Formulations 1–3. 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 with 0.01 w/v% of tyloxapol. This differs from the value recited in claim 19 by a factor of 2.

The '011 patent teaches aqueous ophthalmic formulations containing NSAIDs, BAC and 0.02 w/v% of Octoxynol 40. *See Example 7.*

In the alternative, the '343 patent describes an ophthalmic formulation containing diclofenac (an acidic NSAID), BAC, and tyloxapol with express disclosure tyloxapol concentrations of 1.0 mg/ml and 0.1 mg/ml, *i.e.*, 1 and 0.1 w/v%, in Examples 2 and 3 respectively. Thus, the '343 patent's disclosure of 0.1 w/v% of tyloxapol is a species within the genus of claimed tyloxapol ranges of claims 3 and dependent claims.

In the specification of the '431 Patent, it is reported that a solution of sodium 2-amino-3-(4-bromobenzoyl)phenylacetate (bromfenac sodium) and BAC in an eye drop is less stable in the presence of a tyloxapol surfactant at a concentration of 0.15g/100 ml (0.15 w/v%) than in the presence of a tyloxapol surfactant at a concentration of 0.02g/100 ml (0.15 w/v%). *'431 Patent*, Table 1; col. 7, ll. 57-64. However, there is no evidence that there is any difference in stability in the presence of a tyloxapol surfactant at a concentration of 0.02 w/v%, compared to a tyloxapol

surfactant at a concentration of concentration of 0.01g/100 ml. Accordingly, the Patentee has failed to show that a tyloxapol concentration of 0.02 w/v% is critical, compared to the prior art concentration of 0.01 w/v%.

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

Accordingly, it would have been obvious to a person of ordinary skill in the art to optimize the concentration of tyloxapol provided in the '804 publication or use the known amount of Octoxynol 40, i.e. 0.02 w/v% taught by the '011 patent. 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. Alternatively, 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, Yuan, and the '541 patent. In another alternative, claim 20 is invalid under 35 U.S.C. § 103(a) as obvious over the '225 patent in view the '343 patent and the '609 patent. In a further alternative, claim 20 is invalid under 35 U.S.C. § 103(a) as obvious over the '343 patent in view of the '225 patent and Hara.

xiii) Dependent Claims 21 and 22 of the '446 Patent are obvious under 35 U.S.C. § 103 over (A) the '225 Patent in view of the '804 Publication, the '011 Patent, and Regev or alternatively, (B) the '225 Patent in view of the '804 Publication, the '011 Patent, Yuan, and the '541 patent, or alternatively, (C) the '225 Patent in view the '343 Patent and the '609 Patent, or alternatively, (D) the '343 Patent in view of the '225 Patent and Hara

Claim 21 depends from claim 20, and further limits claim 20 by reciting that the concentration of the bromfenac sodium salt is about 0.01 w/v %.

Claim 22 depends from claim 20, and further limits claim 20 by reciting that the concentration of the bromfenac sodium salt is about 0.1 w/v %.

The '225 patent recites that "[t]he concentrations of the compounds of the invention [benzoylphenylacetic acids] varies depending on symptoms and so on, and usually may be in the range of about 0.001 to about 10%, preferably about 0.01 to about 5%." *'225 patent*, col. 3, ll. 65-68. Thus, the '225 patent discloses that benzoylphenylacetic acid compounds, such as bromfenac, may be used in a range of about 0.01 to about 5%. This range encompasses the claimed concentrations of about 0.01 w/v % (claim 21) and about 0.1 w/v % (claim 22). The Federal Circuit has held that "a prior art reference that discloses a range encompassing a somewhat narrower claimed range is sufficient to establish a *prima facie* case of obviousness." *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003).

Since the prior art teaches the range of bromfenac that encompasses the claimed amounts, claims 21–22 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. Alternatively, claims 21–22 are invalid under 35 U.S.C. § 103(a) as obvious over the '225 patent in view of the '804 publication, the '011 patent,

Yuan, and the '541 patent. In another alternative, claims 21–22 are invalid under 35 U.S.C. § 103(a) as obvious over the '225 patent in view the '343 patent and the '609 patent. In a further alternative, claims 21–22 are invalid under 35 U.S.C. § 103(a) as obvious over the '343 patent in view of the '225 patent and Hara.

4. Secondary Considerations of Nonobviousness

Objective evidence or secondary considerations may serve to rebut a determination that a claim is obvious. Such secondary considerations may include unexpected results, commercial success, longfelt need, failure of others, copying by others, licensing, and skepticism of experts. *Graham,* 383 U.S. at 17-18.

Although a showing of unexpected results may contribute to negating obviousness, such a showing is only probative if: (1) there is actually a difference between the results obtained and those of the closest prior art; and (2) the difference would not have been expected by the skilled artisan at the time of the invention. *In re Freeman*, 474 F.2d 1318, 1324 (C.C.P.A. 1973). "[W]hen unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art." *Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991).

In the specification of the '431 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. *'431 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.

With respect to commercial success, the '431 Patent is listed in the FDA Orange Book with regard to the brand product PROLENSA™. 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® had non-patent exclusivity through October 16, 2013. According to a press release issued on May 27, 2012, the manufacturer of BROMDAY ® discontinued BROMDAY ® in favor PROLENSA ™, which has patent coverage through 2025. It is apparent from this strategy that any commercial success associated with PROLENSA ™ would be based on the market share built through XIBROM ® and BROMDAY ®, and would not have any nexus to the claims of the '431 Patent. Therefore, the commercial success, if any, would not overcome the *prima facie* case of obviousness set forth above.

5. Invalidity of U.S. Patent No. 8,669,290

As explained in detail below, prior to the 102(b) date of the '290 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.

For at least the reasons below, the manufacture, use, offer to sell, or sale of Innopharma's proposed Bromfenac Sodium product, which is the subject of ANDA No. 206-326, will not infringe any valid and enforceable claim of the '290 Patent.

a) Invalidity Analysis of the '290 Patent

i) The Scope and Content of the Prior Art

The scope and content of the prior art is provided above.

b) Differences between the Prior Art and the Claims of the '290 Patent

i) Independent Claims 1 and 14 of the '290 Patent are obvious under 35 U.S.C. § 103 over the '225 Patent in view of the '804 Publication, the '011 Patent, and Regev

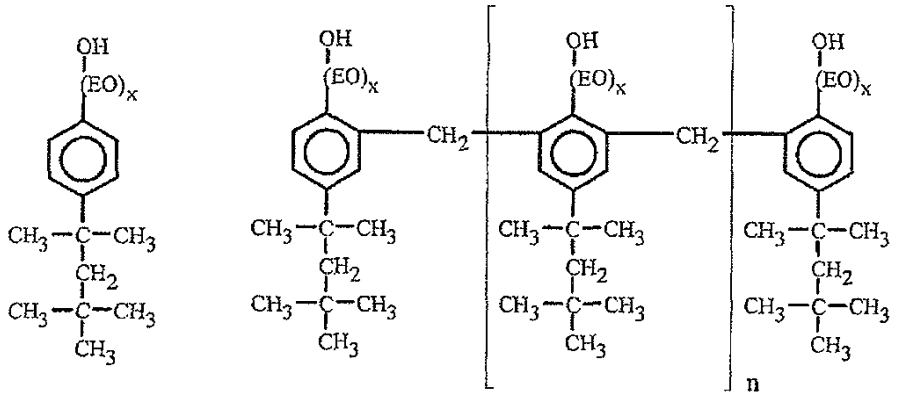
Claim 1 recites an aqueous liquid preparation comprising 2-amino-3-(4-bromobenzoyl)phenylacetic acid (bromfenac) as the sole active ingredient; and tyloxapol. Bromfenac is further characterized as being present in the form of the free acid, a pharmacologically acceptable salt thereof, or a hydrate thereof. 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, and contains tyloxapol in an amount purportedly effective to stabilize bromfenac.

Claim 14 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.

The specification defines tyloxapol as an alkyl aryl polyether alcohol type polymer. *'290 patent, Abstract.*

The formulation of claims 1 and 14 may additionally contain one or more additives such as a buffer, thickener, stabilizer, chelating agent, or pH controlling agent. *Id., col. 6, ll. 9-24.* The buffer may be boric acid and/or sodium borate; the thickener may be polyvinylpyrrolidone; the stabilizer may be sodium sulfite; the chelating agent may be sodium edetate; and the pH controlling agent may be sodium hydroxide. *Id.*

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= $-CH_2CH_2O-$).

During prosecution of the '290 Patent, the language "the first component [bromfenac] is the sole pharmaceutical active ingredient contained in the preparation" was introduced to define over prior art reciting a second active ingredient, in addition to an NSAID. *Prosecution History of the '290 Patent (Exhibit 5)*, Response dated October 22, 2013. Applicants defined over the prior art on the grounds that the cited art purportedly did "not teach or suggest any preparation comprising bromfenac as the sole pharmaceutical active ingredient." *Id.*

Accordingly, claims 1 and 14 require an aqueous liquid preparation comprising bromfenac and tyloxapol, where claim 1 requires that tyloxapol is present in an amount effective to stabilize bromfenac. Claims 1 and 14 exclude active ingredients other than bromfenac. Claim 14 further excludes mannitol.

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

EXAMPLE 6

Ophthalmic Solution

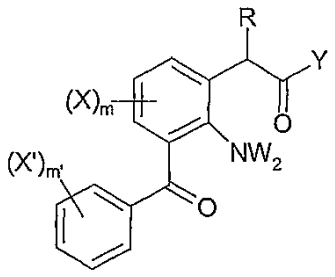
Sodium 3-(4-bromobenzoyl)-2-aminophenyl-acetate monohydrate	0.1 g
Boric acid	1.25 g
Borax	1.0 g
Disodium edetate	0.02 g
Benzalkonium chloride	0.005 g
Polysorbate 80	0.15 g
Polyvinyl pyrrolidone	2.0 g
Sodium sulfite	0.2 g
Sterile purified water	To make 100 ml
pH 8	

Id., Example 6. The formulation of Example 6 does not include mannitol, as required by claim 14.

Accordingly, Example 6 of the '225 patent purportedly describes an aqueous liquid preparation comprising the monohydrate of the sodium salt of bromfenac; polysorbate 80; benzalkonium chloride; and various biologically inactive additives. Example 6 does not include active ingredients other than bromfenac.

The only difference between Example 6 of the '225 patent and claims 1 and 14 of the '290 Patent is the nonionic surfactant, i.e. polysorbate 80 rather than tyloxapol. The '290 Patent asserts that the use of tyloxapol instead of polysorbate 80 surprisingly and significantly improves the stability of the formulation.

However, before the filing of the '290 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 claims 1 and 14 of the '290 Patent again is the presence of polysorbate 80 instead of tyloxapol. .

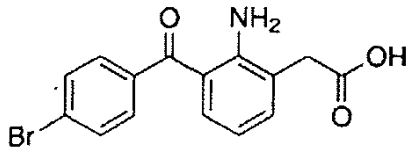
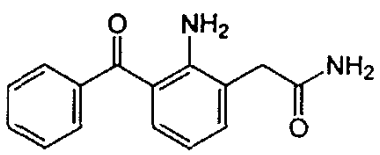
The '804 publication also describes a topical formulation comprising a derivative of 3-benzoylphenylacetic acid, nepafenac, as the sole active ingredient; tyloxapol; and benzalkonium chloride. *Id.*, Formulation 3 on page 7. Formulation 3 has the following constituents:

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%

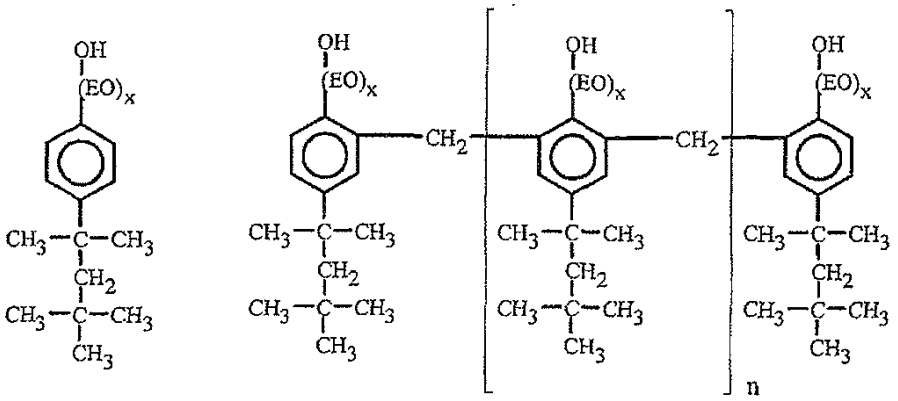
Thus, the difference between this formulation and that of claims 1 and 14 of the '290 Patent is the presence of nepafenac instead of bromfenac. Nepafenac differs from bromfenac in the absence of a bromine substitution and the presence of an acetamide rather than the carboxylic acid as shown below:

Bromfenac	**Nepafenac**
	

Moreover, the '804 publication teaches the substitutability of tyloxapol for polysorbate 80 as a surfactant for aqueous ophthalmic solutions, including bromfenac generically.

It was therefore known at the time of filing the '290 Patent 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." *Id.*, 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. *'011 patent*, 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 in the art 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 '290 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).



Triton X-100 Tyloxapol

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

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

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.[9] 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 would have been motivated to modify the 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

[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) (Exhibit 16).*

combination of the prior art teaches all of the elements of claims 1 and 14, and claims 1 and 14 is *prima facie* obvious over the prior art.

ii) Independent Claims 1 and 14 of the '290 Patent are obvious under 35 U.S.C. § 103 over the '225 Patent in view of the '804 Publication, the '011 Patent, Yuan, and the '541 Patent

As discussed *supra*, the formulation of Example 6 of the '225 patent differs from the formula-tion of claims 1 and 14 in that it contains the nonionic surfactant polysorbate 80 rather than the nonionic surfactant tyloxapol.

Also 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.

Also as discussed above, the '011 patent teaches 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 in the art 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 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.

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 would have been motivated in view of the '804 publication, the '011 patent, Yuan, and the '541 patent to replace polysorbate 80 with tyloxapol, the combination of the prior art teaches all of the elements of claims 1 and 14, and claims 1 and 14 would have been *prima facie* obvious over the prior art.

iii) Independent Claims 1 and 14 of the '290 Patent are obvious under 35 U.S.C. § 103 over the '225 Patent in view of the '343 Patent and the '609 Patent, or alternatively, over the '343 Patent in view of the '225 Patent and Hara

As discussed *supra*, the formulation of Example 6 of the '225 patent differs from the formulation of claims 1 and 14 in that it contains the nonionic surfactant polysorbate 80 rather than the nonionic surfactant tyloxapol.

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

EXAMPLE 2

Formulation of diclofenac potassium eye drops (0.05%)

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

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

Further, neither Example 6 in the '225 patent nor Example 2 of the '343 patent contain mannitol as required in claim 14 of the '290 Patent.

A person of ordinary skill in the art would have had reason to combine the '225 and '343 patents to arrive at the formulation recited in claims 1 and 14 as it was known prior to the '290 patent that acidic NSAIDs (such as bromfenac) containing an ionizable carboxylic acid group form complexes with quaternary ammonium preservatives, such as BAC in ophthalmic formulations. The interaction of the NSAID with BAC results in complexes that were known to precipitate out of the ophthalmic formulation, which is problematic because it (1) renders the preservative (e.g., BAC) less available to serve its function and (2) reduces the availability of the NSAID (e.g., bromfenac).

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

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

In addition it was also known that tyloxapol was a preferred or better solubilizer than polysorbate 80 for acidic compounds in aqueous ophthalmic formulations. The '343 patent

teaches that tyloxapol is a preferred solubilizer. *'343 patent*, col. 4, l. 62. The '609 patent further provides motivation to use tyloxapol over polysorbate. Specifically, the '609 patent teaches that tyloxapol is superior to polysorbate 80 in solubilizing acidic ophthalmic drugs:

TABLE 4

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

TABLE 4-continued

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

*polyoxyethylene hydrogenated castor oil 60
**butylated hydroxytoluene

TABLE 5

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

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

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

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

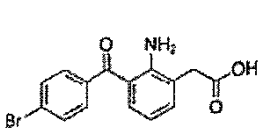
Accordingly, a person of ordinary skill would have had motivation to substitute, and a reasonable expectation of success in substituting, tyloxapol for polysorbate 80 because the prior art such as the '343 patent provides an example of stable aqueous preparations containing NSAIDs (similar to bromfenac) formulated with BAC and tyloxapol (and other closely related non-ionic surfactants). Further, a person of ordinary skill would have had motivation to prepare a bromfenac ophthalmic formulation containing tyloxapol as the surfactant because tyloxapol was the best solubilizing agent used to stabilize an ophthalmic pranlukasut formulation according to the '609 patent. "[W]hen a patent 'simply arranges old elements with each performing the same function it had been known to perform' and yields no more than one would expect from such an arrangement, the combination is obvious." *KSR*, 550 U.S. at 416 (citing *Sakraida v. AG Pro, Inc.*, 425 U.S. 273 (1976)).

Since a person of ordinary skill in the art would have been motivated in view of the '343 and '609 patents, to replace polysorbate 80 with tyloxapol, the combination of the prior art teaches all of the elements of claim 1 and 14, and claim 1 and 14 are *prima facie* obvious over the prior art.

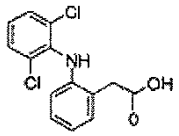
As an alternative to switching nonionic surfactants in the aqueous ophthalmic preparations of the '225 and '343 patents, it would have also been obvious to switch NSAIDs. Thus, it would have been obvious to use bromfenac from the '225 patent's Example 6 instead of diclofenac in the '343 patent's Example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

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

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



Bromfenac



Diclofenac

[redacted]

Hara describes bromfenac as superior to diclofenac and provides a person of ordinary skill in the art a reason to substitute the diclofenac in the '343 patent's Example 2 with the bromfenac in the '225 patent's Example 6.

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

A person of ordinary skill would have had a reason to combine the teachings of the '343 and '225 patents because the '343 patent teaches an aqueous liquid ophthalmic formulation of diclofenac formulated with tyloxapol and benzalkonium chloride, and Hara teaches that bromfenac [sodium hydrate] as disclosed in the '225 patent, is broadly applicable for treatment of various ophthalmic conditions, and preferable as compared to diclofenac. Thus, a person of ordinary skill in the art, reading '343 and '225 patents, would have had a reason to substitute the bromfenac of '225 patent's Example 6 for diclofenac in '343 patent's Example 2.

A person of ordinary skill would have known that substituting bromfenac for diclofenac would have yielded predictable results because both are NSAIDs with similar pharmacological properties. Furthermore, a person of ordinary skill in the art facing a design need to formulate a stable bromfenac solution would have found it at least obvious to try to prepare an aqueous liquid bromfenac preparation comprising tyloxapol because Hara teaches that there were only four NSAID ophthalmic drugs available on the market by 2003, "resulting in limited choices." Hara, 1014:2:2. Therefore, in view of the '343 and '225 patents and in further view of Hara, a person of ordinary skill in the art would have reasonably expected to be able to make and use an aqueous liquid ophthalmic preparation within the scope of claims 1 and 14 of the '290 Patent and accordingly, claims 1 and 14 are invalid.

iv) Independent Claim 8 of the '290 Patent is obvious under 35 U.S.C. § 103 over the '225 Patent in view of the '804 Publication, the '011 Patent, and Regev or, alternatively, in view of the '804 Publication, the '011 Patent, Yuan, and the '541 patent

Claim 8 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 the first component is the sole pharmaceutical active ingredient contained in the preparation; and
>
> (b) a second component, where the second component is tyloxapol;
>
> wherein said stable liquid preparation is formulated for ophthalmic administration.

The scope of claim 8 is substantially similar to claim 1, except that claim 8 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 8 does not include the limitation of claim 1 that tyloxapol is present in an amount effective to stabilize the first component.

Accordingly, claim 8 requires an aqueous liquid preparation comprising a salt or hydrate of bromfenac and tyloxapol, where 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.

As discussed above with regard to claims 1 and 14, the '225 patent discloses, in Example 6, an ophthalmic formulation containing the following ingredients:

EXAMPLE 6

Ophthalmic Solution

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

'225 patent, Example 6.

With regard to Examples 6–8 generally, "[i]t was found that changes in the appearances of the compositions were not observed at all, and the decomposition of the compound was not almost observed [sic], the aqueous compositions being stable, excellent [sic] for a long period of time." *See id. col. 10, ll. 50–57, and col. 14, ll. 45-48 (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. *See id. Table 11.*

Also as discussed above with regard to claims 1 and 14, 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 claims 1 and 14, 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 in the formulation of Example 6 of the '225 patent.

Accordingly, the combination of ingredients in the formulation of claim 8 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 in the art would have found enhanced stability to be an inherent property of a formulation containing a nonionic polyoxyethylated octylphenol surfactant, such as Tyloxapol. 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 8 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 8 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.

v) Independent Claim 8 of the '290 Patent is obvious under 35 U.S.C. § 103 over the '225 Patent in view of the '343 Patent and the '609 Patent, or alternatively, over the '343 Patent in view of the '225 Patent and Hara

As discussed above, limitations of claim 8 which are common to claim 1 are obvious over the '225 patent's Example 6 in view of the '343 patent's Example 2 for the same reasons discussed above for claim 1.

With regard to the limitation of claim 8 requiring that "greater than about 90 %" of the original bromfenac remains after storage at 60° C for 4 weeks, the '225 patent's describes that in 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." *See id. col. 10,*

ll. 50–57, and col. 14, ll. 45-48 (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. *See id. Table 11.*

Thus, a person of ordinary skill in the art would reasonably expect that switching surfactants, and employing the tyloxapol from the '343 patent's Example 2 instead of polysorbate 80 in the '225 patent's Example 6, would maintain greater than about 90% stability after 4 weeks at 60° C. as recited in claim 8. *Id.*

Accordingly, claim 8 is invalid under 35 U.S.C. § 103(a) as obvious over the '225 patent in view the '343 patent and the '609 patent; and as obvious over the '343 patent in view of the '225 patent and Hara.

vi) Dependent Claims 10, 20 and 22 of the '290 Patent are obvious under 35 U.S.C. § 103 over (A) the '225 Patent in view of the '804 Publication, the '011 Patent, and Regev or alternatively, (B) the '225 Patent in view of the '804 Publication, the '011 Patent, Yuan, and the '541 patent, or alternatively, (C) the '225 Patent in view the '343 Patent and the '609 Patent, or alternatively, (D) the '343 Patent in view of the '225 Patent and Hara

Claim 10 depends from claim 8, and further limits claim 8 by reciting that the stable aqueous liquid preparation is characterized in that greater than about 92% of the original amount of the first component remains in the preparation after storage at about 60° C. for 4 weeks.

Claim 20 depends from claim 14, and further limits claim 14 by reciting 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 22 depends from claim 20, and further limits claim 20 by reciting 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.

Thus, claims 10, 20, and 22 each further limit their respective base claims only by reciting a property of storage stability.

Claims 8 and 14, from which claims 10, 20, and 22 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.

Accordingly, according to *Santarus*, mere recitation of an inherent stability is insufficient to render an otherwise obvious compound patentable; therefore claims 10, 20, 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; and as obvious over the '225 patent in view of the '804 publication, the '011 patent, Yuan, and the '541 patent. In another alternative, claims 10, 20, and 22 are invalid under 35 U.S.C. § 103(a) as obvious over the '225 patent in view the '343 patent and the '609 patent. In a further alternative, claims 10, 20, and 22 are invalid under 35 U.S.C. § 103(a) as obvious over the '343 patent in view of the '225 patent and Hara.

vii) Dependent Claims 2, 9, 15 and 21 of the '290 Patent are obvious under 35 U.S.C. § 103 over (A) the '225 Patent in view of the '804 Publication, the '011 Patent, and Regev or alternatively, (B) the '225 Patent in view of the '804 Publication, the '011 Patent, Yuan, and the '541 patent, or alternatively, (C) the '225 Patent in view the '343 Patent and the '609 Patent, or alternatively, (D) the '343 Patent in view of the '225 Patent and Hara

Claims 2, 9, 15, and 21 depend from claims 1, 8, 14, and 20 and further limit their respective base claims by reciting that the claimed composition further comprises a quaternary ammonium salt.

The specification of the '225 patent describes benzalkonium chloride as a quaternary ammonium compound having a preservative effect. *'225 patent, col. 2, ll. 4-10.*

Example 6 of the '225 patent describes an aqueous liquid preparation comprising the monohydrate of the sodium salt of bromfenac; polysorbate 80; and the quaternary ammonium salt benzalkonium chloride, as required by claim 2. *Id.,* Example 6. The '011 patent teaches the use of specific surfactants to further stabilize NSAID and BAC formulations. In addition, the '343 patent's Examine 2 include BAC in its described NSAID formulation.

Accordingly, claims 2, 9, 15, 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. Alternatively, claims 2, 9, 15, 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, Yuan, and the '541 patent. In another alternative, claims 2, 9, 15, and 21 are invalid under 35 U.S.C. § 103(a) as obvious over the '225 patent in view the '343 patent and the '609 patent. In a further alternative, claims 2, 9, 15, and 21 are invalid under 35 U.S.C. § 103(a) as obvious over the '343 patent in view of the '225 patent and Hara.

viii) Dependent Claims 3 and 16 of the '290 Patent are obvious under 35 U.S.C. § 103 over (A) the '225 Patent in view of the '804 Publication, the '011 Patent, and Regev or alternatively, (B) the '225 Patent in view of the '804 Publication, the '011 Patent, Yuan, and the '541 patent, or alternatively, (C) the '225 Patent in view the '343 Patent and the '609 Patent, or alternatively, (D) the '343 Patent in view of the '225 Patent and Hara

Claims 3 and 16 depend from claim 1 and 14, 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.

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.

Accordingly, claims 3 and 16 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. Alternatively, claims 3 and 16 are invalid under 35 U.S.C. § 103(a) as obvious over the '225 patent in view of the '804 publication, the '011 patent, Yuan, and the '541 patent. In another alternative, claims 3 and 16 are invalid under 35 U.S.C. § 103(a) as obvious over the '225 patent in view the '343 patent and the '609 patent. In a further alternative, claims 3 and 16 are invalid under 35 U.S.C. § 103(a) as obvious over the '343 patent in view of the '225 patent and Hara.

ix) Dependent Claims 4, 11, 17 and 23 of the '290 Patent are obvious under 35 U.S.C. § 103 over (A) the '225 Patent in view of the '804 Publication, the '011 Patent, and Regev or alternatively, (B) the '225 Patent in view of the '804 Publication, the '011 Patent, Yuan, and the '541 patent, or alternatively, (C) the '225 Patent in view the '343 Patent and the '609 Patent, or alternatively, (D) the '343 Patent in view of the '225 Patent and Hara

Claims 4, 11, 17, and 23 depend from claims 1, 8, 16, and 20, 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 %.

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 4, 11, 17, and 23. *'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 4, 11, 17, and 23. *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.[10] 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 in the art to modify the formulation of Example 6 of the '225 patent by replacing polysorbate 80 in a concentration of 0.15 w/v%, as used by the '225 patent, with 0.01 w/v% of tyloxapol, as encompassed by claims 4, 11, 17, and 23.

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

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

Accordingly, claims 4, 11, 17, and 23 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. Alternatively,

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

claims 4, 11, 17, and 23 are invalid under 35 U.S.C. § 103(a) as obvious over the '225 patent in view of the '804 publication, the '011 patent, Yuan, and the '541 patent. In another alternative, claims 4, 11, 17, and 23 are invalid under 35 U.S.C. § 103(a) as obvious over the '225 patent in view the '343 patent and the '609 patent. In a further alternative, claims 4, 11, 17, and 23 are invalid under 35 U.S.C. § 103(a) as obvious over the '343 patent in view of the '225 patent and Hara.

x) Dependent Claim 5 of the '290 Patent is obvious under 35 U.S.C. § 103 over (A) the '225 Patent in view of the '804 Publication, the '011 Patent, and Regev or alternatively, (B) the '225 Patent in view of the '804 Publication, the '011 Patent, Yuan, and the '541 patent, or alternatively, (C) the '225 Patent in view the '343 Patent and the '609 Patent, or alternatively, (D) the '343 Patent in view of the '225 Patent and Hara

Claim 5 depends from claim 4, and further limits claim 4 by reciting that the concentration of the bromfenac sodium salt is about 0.1 w/v %.

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 3–5 and 11. *'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 required by claims 5. *Id.*, Example 6.

Accordingly, claim 5 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. Alternatively, claim 5 is invalid under 35 U.S.C. § 103(a) as obvious over the '225 patent in view of the '804 publication, the '011 patent, Yuan, and the '541 patent. In another alternative, claim 5 is invalid under 35 U.S.C. § 103(a) as obvious over the '225 patent in view the '343 patent and the '609 patent. In a further alternative, claim 5 is invalid under 35 U.S.C. § 103(a) as obvious over the '343 patent in view of the '225 patent and Hara.

xi) Dependent Claims 6, 12, 18 and 24 of the '290 Patent are obvious under 35 U.S.C. § 103 over (A) the '225 Patent in view of the '804 Publication, the '011 Patent, and Regev or alternatively, (B) the '225 Patent in view of the '804 Publication, the '011 Patent, Yuan, and the '541 patent, or alternatively, (C) the '225 Patent in view the '343 Patent and the '609 Patent, or alternatively, (D) the '343 Patent in view of the '225 Patent and Hara

Claims 6, 12, 18, and 24 depends from claims 1, 11, 17, and 23, respectively, and further limits their respective base claims by reciting that the pH of the aqueous liquid preparation is from about 7.5 to about 8.5.

The formulation of Example 6 of the '225 patent has a pH of 8, as encompassed by claims 6, 12, 18, and 24. *'225 patent*, Example 6.

In addtion, Hara expressly discloses a pH of 8.0-8.6 which is encompassed by claims 9 and 10. *Hara,* 1015:1:2.

Accordingly, claims 6, 12, 18, 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. Alternatively, claims 6, 12, 18, 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, Yuan, and the '541 patent. In another alternative, claims 6, 12, 18, and 24 are invalid under 35 U.S.C. § 103(a) as obvious over the '225 patent in view the '343 patent and the '609 patent. In a further alternative, claims 6, 12, 18, and 24 are invalid under 35 U.S.C. § 103(a) as obvious over the '343 patent in view of the '225 patent and Hara.

xii) Dependent Claims 7, 13, 19, and 25 of the '290 Patent are obvious under 35 U.S.C. § 103 over (A) the '225 Patent in view of the '804 Publication, the '011 Patent, and Regev or alternatively, (B) the '225 Patent in view of the '804 Publication, the '011 Patent, Yuan, and the '541 Patent, or alternatively, (C) the '225 Patent in view the '343 Patent and the '609 Patent, or alternatively, (D) the '343 Patent in view of the '225 Patent and Hara

Claims 7, 13, 19, and 25 depend from claims 1, 8, 14, and 20, respectively, and further limit their base claims by reciting that the aqueous liquid preparation consists essentially of a 2-amino-3-(4-bromobenzoyl)phenylacetic acid (bromfenac) compound; tyloxapol; boric acid; sodium tetraborate; EDTA sodium salt; benzalkonium chloride; polyvinyl pyrrolidone; and sodium sulfite. Bromfenac is further characterized as being present in the form of the free acid, a pharmacologically acceptable salt thereof, or a hydrate thereof. 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, and contains bromfenac sodium in a concentration of from about 0.02 to about 0.1 w/v %.

Claim 7 requires that the bromfenac compound is bromfenac sodium salt.

Claims 13, 19, and 25 require that the bromfenac compound 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.

Claim 7, 13, 19, and 25 contains the transitional phrase "consists essentially of." The transitional phrase "consists 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).

Accordingly, claim 7, depending from claim 1, requires an aqueous liquid preparation consisting essentially of a sodium salt of bromfenac; tyloxapol; boric acid; sodium tetraborate

(borax); EDTA sodium salt (edetate sodium salt); benzalkonium chloride; polyvinylpyrrolidone; and sodium sulfite. Claim 1 excludes active ingredients other than bromfenac, as discussed above.

Further, claims 13, 19, and 25 requires an aqueous liquid preparation consisting essentially of a salt, hemihydrate, monohydrate, or sesquihydrate of bromfenac; tyloxapol; boric acid; sodium tetraborate (borax); EDTA sodium salt (edetate sodium salt); benzalkonium chloride; polyvinylpyrrolidone; and sodium sulfite. Claim 1 excludes active ingredients other than bromfenac, as discussed above.

Claims 7, 13, 19, and 25 recite a specific list of excipients in the formulation of claim 1. These excipients are all shown by Example 6 of the '225 patent, the only difference being the use of polysorbate 80 instead of tyloxapol, as shown in the table below: Example 6 of the '225 patent recites 0.1 w/v% bromfenac sodium monohydrate, which is both a sodium salt of bromfenac, as required by claim 7, and a monohydrate of bromfenac, as required by claims 13, 19, and 25.

Claim 7 of the '290 patent	**Example 6 of the '225 patent**
Bromfenac sodium (0.01 to 0.2 w/v%)	Bromfenac sodium monohydrate (0.1 w/v%)
Tyloxapol	*Polysorbate 80*
Boric acid	Boric acid
Sodium tetraborate	Borax
EDTA sodium salt	Disodium edetate
Benzalkonium chloride	Benzalkonium chloride
Polyvinylpyrrolidone	Polyvinylpyrrolidone
Sodium sulfite	Sodium sulfite

As discussed above with regard to claim 1, 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.

Similarly, 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, l. 66-col. 3, l. 4. "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 as preferred surfactants for improving the stability of NSAIDs in aqueous solutions containing benzalkonium chloride, such as Example 6 of the '225 patent.

Regev teaches that tyloxapol has a higher cloud point and a lower critical micelle concentration than the corresponding monomeric nonionic polyoxyethylated octylphenol surfactant. Therefore, a person of ordinary skill in the art 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 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.

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

Accordingly, claims 7, 13, 19, and 25 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. Alternatively, claims 7, 13, 19, and 25 are invalid under 35 U.S.C. § 103(a) as obvious over the '225 patent in view of the '804 publication, the '011 patent, Yuan, and the '541 patent. In another alternative, claims 7, 13, 19, and 25 are invalid under 35 U.S.C. § 103(a) as obvious over the '225 patent in view the '343 patent and the '609 patent. In a further alternative, claims 7, 13, 19, and 25 are invalid under 35 U.S.C. § 103(a) as obvious over the '343 patent in view of the '225 patent and Hara.

xiii) Dependent Claims 26-30 of the '290 Patent are obvious under 35 U.S.C. § 103 over (A) the '225 Patent in view of the '804 Publication, the '011 Patent, and Regev or alternatively, (B) the '225 Patent in view of the '804 Publication, the '011 Patent, Yuan, and the '541 Patent, or alternatively, (C) the '225 Patent in view the '343 Patent and the '609 Patent, or alternatively, (D) the '343 Patent in view of the '225 Patent and Hara

Claims 26, 27, 28, 29, and 30 depend from claims 1, 8, 14, 20, and 22, 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. albi-cans, 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 26, 27, 28, 29, and 30 each further limit their respective base claims only by reciting properties of preservative efficacy in the presence of microbes, based on known standards.

Claims 1, 8, 14, 20, and 22, from which claims 26, 27, 28, 29, and 30 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 '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.

A 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 or from general common knowledge. 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.*

Accordingly, claim 26, 27, 28, 29, and 30 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 alternatively, as obvious over the '225 patent in view of the '804 publication, the '011 patent, Yuan, and the '541 patent. In another alternative, claim 26, 27, 28, 29, and 30 are invalid under 35 U.S.C. § 103(a) as obvious over the '225 patent in view the '343 patent and the '609 patent. In a further alternative, claim 26, 27, 28, 29, and 30 are invalid under 35 U.S.C. § 103(a) as obvious over the '343 patent in view of the '225 patent and Hara.

c) Secondary Considerations of Nonobviousness

In the specification of the '290 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. *'290 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.

With respect to commercial success, the '290 Patent is listed in the FDA Orange Book with regard to the brand product PROLENSA™. 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. According to a press release issued on May 27, 2012, BROMDAY® was discontinued in favor of PROLENSA™, which has patent coverage through 2025. Moreover, PROLENSA™ has received non-patent exclusivity as a new product through April 5, 2016. Based on the marketing strategy and non-patent exclusivity, any commercial success associated with PROLENSA™ would be based on the market share built through XIBROM® and BROMDAY®, and would not have any nexus to the claims of the '290 Patent. Therefore, the commercial success, if any, would not overcome the *prima facie* case of obviousness set forth above.

D. NON-INFRINGEMENT OF THE '431 PATENT

As set forth in detail above, each of claims of the '431 patent is invalid under 35 U.S.C. § 103. Accordingly, because the claims of the '431 patent are invalid, Innopharma cannot infringe any of these claims.

E. NON-INFRINGEMENT OF THE '290 PATENT

As set forth in detail above, each of claims of the '290 patent is invalid under 35 U.S.C. § 103. Accordingly, because the claims of the '290 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
Kwadwo (Kojo) Awuah, PharmD., RAC
LCDR, US Public Health Service
Deputy Director (Acting)
Division of Filing Review
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