Watson

June 1, 2015

Via Certified Mail and/or FedEx®

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Warren M. Cheek, Jr., Esq.
Wenderoth, Lind & Ponack, L.L.P.
1030 15th St., NW, Suite 400 East
Washington, DC 20005

HIGHLY CONFIDENTIAL

Re: Notification of Certification for U.S. Patent Nos. 8,129,431, 8,669,290, 8,754,131, 8,871,813 and 8,927,606 Pursuant to § 505(j)(2)(B)(iv) of the Federal Food, Drug, and Cosmetic Act

Dear Madam or Sir:

Pursuant to § 505(j)(2)(B)(iv) of the Federal Food, Drug, and Cosmetic Act and 21 C.F.R. § 314.95, Watson Laboratories, Inc. ("Watson") hereby provides notice of the following information to: (i) Bausch & Lomb ("Bausch & Lomb"), as the apparent holder of approved New Drug Application ("NDA") No. 203168 for Prolensa™ (bromfenac sodium) Ophthalmic Solution, Eq. 0.07% Acid according to the records of the U.S. Food and Drug Administration ("FDA") and Senju Pharmaceutical Co., Ltd ("Senju"), as the record owner of U.S. Patent Nos. 8,129,431, 8,669,290, 8,754,131, 8,871,813, and 8,927,606 according to the records of the U.S. Patent and Trademark Office ("PTO") and/or the face of the patent.

As a courtesy, Watson provides a copy of this Notice Letter and Detailed Statement to Warren M. Cheek, Jr., Esq. of Wenderoth, Lind & Ponack, L.L.P. as the correspondent for U.S. Patent Nos. 8,129,431; 8,669,290; 8,754,131; 8,871,813; and 8,927,606 according to the records

of the PTO and/or the face of the patent.

Pursuant to 21 C.F.R. § 314.95(e), Watson requested from FDA permission to send this notice by means other than registered or certified mail. Specifically, Watson requested that it be allowed to send this notice by FedEx®. Consequently, the operative date for determining the start of the 45-day clock under 21 U.S.C. § 355(j)(5)(B)(iii) began from the receipt of this notice, as sent via FedEx® and/or Certified Mail.

I. Pursuant to 21 U.S.C. § 355(j)(2)(B)(iv)(I) and 21 C.F.R. § 314.95(c)(1), we advise you that FDA has received an Abbreviated New Drug Application ("ANDA") from Watson for Bromfenac Ophthalmic Solution, 0.07%. The ANDA contains the required bioavailability and/or bioequivalence data and/or bioequivalence waiver. The ANDA was submitted under 21 U.S.C. § 355(j)(1) and (2)(A), and contains Paragraph IV certifications to obtain approval to engage in the commercial manufacture, use or sale of Bromfenac Ophthalmic Solution, 0.07%, before the expiration of U.S. Patent Nos. 8,129,431; 8,669,290; 8,754,131; 8,871,813; and 8,927,606 which are listed in the Patent and Exclusivity Information Addendum of FDA's publication, *Approved Drug Products with Therapeutic Equivalence Evaluations* (commonly known as the "Orange Book").

II. Pursuant to 21 C.F.R. § 314.95(c)(2), we advise you that FDA has assigned Watson's ANDA the number 206085.

III. Pursuant to 21 C.F.R. § 314.95(c)(3), we advise you that the established name of the drug product that is the subject of Watson's ANDA is Bromfenac Ophthalmic Solution, 0.07%.

IV. Pursuant to 21 C.F.R. § 314.95(c)(4), we advise you that the active ingredient in the proposed drug product is bromfenac sodium; the strength of the proposed drug product is 0.07% of bromfenac; and the dosage form of the proposed drug product is ophthalmic solution.

V. Pursuant to 21 C.F.R. § 314.95(c)(5), we advise you that the patents alleged to be invalid, unenforceable, and/or not infringed in the Paragraph IV certifications are U.S. Patent Nos. 8,129,431; 8,669,290; 8,754,131; 8,871,813; and 8,927,606 which are listed in the Orange Book in connection with Bausch & Lomb's approved NDA No. 203168 for Prolensa™. According to information published in the Orange Book, the patents will expire as follows:

U.S. PATENT NO.	EXPIRATION DATE
8,129,431	September 11, 2025
8,669,290	January 16, 2024
8,754,131	January 16, 2024
8,871,813	January 16, 2024

U.S. PATENT NO.	EXPIRATION DATE
8,927,606	January 16, 2024

VI. Watson alleges, and has certified to FDA, that in Watson's opinion and to the best of its knowledge, U.S. Patent Nos. 8,129,431; 8,669,290; 8,754,131; 8,871,813; and 8,927,606 are invalid, unenforceable, and/or will not be infringed by the commercial manufacture, use or sale of the drug product described in Watson's ANDA. Therefore, pursuant to 21 U.S.C. § 355(j)(2)(B)(iv)(II) and 21 C.F.R. § 314.95(c)(6), Watson's detailed statement of the legal and factual basis for the Paragraph IV certifications set forth in Watson's ANDA is attached hereto and made a part hereof.

VII. Pursuant to 21 U.S.C. § 355(j)(5)(C), this notice letter includes an Offer of Confidential Access to Application. As required by § 355(j)(5)(C)(i)(III), Watson offers to provide confidential access to certain information from its ANDA No. 206085 for the sole and exclusive purpose of determining whether an infringement action referred to in § 355(j)(5)(B)(iii) can be brought.

Section 355(j)(5)(C)(i)(III) allows Watson 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 Watson the right to redact its ANDA in response to a request for Confidential Access under this offer.

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

(1) Watson will permit confidential access to certain information from its proprietary ANDA No. 206085 to attorneys from one outside law firm representing Bausch & Lomb and one outside law firm representing Senju, provided however that such attorneys do not engage, formally or informally, in any patent prosecution for Bausch & Lomb or Senju or any FDA counseling, litigation or other work before or involving FDA. Such information (hereinafter, "Confidential Watson Information") shall be marked with the legend "CONFIDENTIAL."

(2) The attorneys from the outside law firms representing Bausch & Lomb and/or Senju shall not disclose any Confidential Watson Information to any other person or entity, including employees of Bausch & Lomb or Senju, outside scientific consultants, and/or other outside counsel retained by Bausch & Lomb or Senju, without the prior written consent of Watson.

(3) As provided by § 355(j)(5)(C)(i)(III), the outside law firms representing Bausch & Lomb or Senju shall make use of the Confidential Watson Information for the sole and exclusive purpose of determining whether an action referred to in § 355(j)(5)(B)(iii) can be brought — and for no other purpose. By way of

example only, the Confidential Watson Information shall not be used to prepare or prosecute any future or pending patent application by Bausch & Lomb or Senju; in connection with any filing to, or communication with, FDA relating to Watson's ANDA No. 206085; or in connection with any submission to, or communication with, the United States Pharmacopeia or any similar organization. The outside law firms representing Bausch & Lomb or Senju agree to take all measures necessary to prevent unauthorized disclosure or use of the Confidential Watson Information, and that all Confidential Watson Information shall be kept confidential and not disclosed in any manner inconsistent with this Offer of Confidential Access.

(4) The Confidential Watson Information disclosed is, and remains, the property of Watson. By providing the Confidential Watson Information, Watson does not grant Bausch & Lomb or Senju and/or their outside law firms any interest in or license for the Confidential Watson Information.

(5) The outside law firms representing Bausch & Lomb or Senju shall, within thirty-five (35) days from the date that it first receives the Confidential Watson Information, return to Watson all Confidential Watson Information and any copies thereof. Said outside law firm shall return all Confidential Watson Information before any infringement suit is filed by Bausch & Lomb and/or Senju, if suit is commenced before this 35-day period expires. In the event that Bausch & Lomb and/or Senju opts to file suit, none of the information contained in or obtained from any Confidential Watson Information that Watson provides 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 Watson regarding the validity, enforceability, and/or infringement of any U.S. patent. Further, nothing herein shall be construed as an agreement or admission by Watson with respect to the competency, relevance, or materiality of any such Confidential Watson Information, document, or thing. The fact that Watson provides Confidential Watson Information upon request of Bausch & Lomb or Senju shall not be construed as an admission by Watson that such Confidential Watson Information is relevant to the disposition of any issue relating to any alleged infringement of or to the validity or enforceability of U.S. Patent Nos. 8,129,431; 8,669,290; 8,754,131; 8,871,813; and 8,927,606.

(7) The attorneys from the outside law firms representing Bausch & Lomb or Senju shall acknowledge in writing their receipt of a copy of these terms and restrictions prior to production of any Confidential Watson Information. Such written acknowledgement shall be provided to Watson.

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

Section 355(j)(5)(C)(i)(III) provides that any request for access that Bausch & Lomb or Senju makes under this Offer of Confidential Access "shall be considered acceptance of the offer of confidential access with the 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 Bausch & Lomb or Senju request access to Confidential Watson Information, it necessarily accepts the terms and restrictions outlined above. Written notice requesting access under this Offer of Confidential Access should be made to:

Brian Anderson, Esq.
Morris Corporate Center III
400 Interpace Parkway
Parsippany, NJ 07054
(862) 261-8406
brian.anderson@actavis.com

By providing this Offer of Confidential Access to Application, Watson 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).

Very truly yours,

Watson Laboratories, Inc.

By: Joyce Anne Delgaudio
Executive Director, Regulatory Affairs

Enclosure: *Watson's Detailed Factual and Legal Basis for Its Paragraph IV Certifications that U.S. Patent Nos. 8,129,431, 8,669,290, 8,754,131, 8,871,813, and 8,927,606 are Invalid, Unenforceable and/or Not Infringed by the Bromfenac Product Described in Watson's ANDA No. 206085*

ENCLOSURE

WATSON'S DETAILED FACTUAL AND LEGAL BASIS FOR ITS PARAGRAPH IV CERTIFICATIONS THAT U.S. PATENT NOS. 8,129,431; 8,669,290; 8,754,131; 8,871,813; AND 8,927,606 ARE INVALID, UNENFORCEABLE AND/OR NOT INFRINGED BY THE BROMFENAC PRODUCT DESCRIBED IN WATSON'S ANDA NO. 206085

Pursuant to § 505(j)(2)(B)(iv)(II) of the Federal Food, Drug, and Cosmetic Act and 21 C.F.R. § 314.95(c)(6), the following information comprises the detailed factual and legal basis for the Paragraph IV certifications of Watson Laboratories, Inc. (Watson) that, in its opinion and to the best of its knowledge, U.S. Patent Nos. 8,129,431 ("the '431 patent"), 8,669,290 ("the '290 patent"), 8,754,131 ("the '131 patent"), 8,871,813 ("the '813 patent"), and 8,927,606 ("the '606 patent") are invalid, unenforceable and/or will not be infringed by the commercial manufacture, use, sale, offer for sale or importation of the drug product described in Watson's ANDA No. 206085 ("Watson's ANDA Product" or "the Watson ANDA Product"). Watson reserves all rights to raise additional defenses relating to invalidity, unenforceability and/or non-infringement should litigation ensue.

I. WATSON'S ANDA PRODUCT

The Watson ANDA Product is an ophthalmic solution containing 0.07 mg/mL of bromfenac.

The composition of Watson's ANDA Product may be disclosed pursuant to the terms set forth in the Offer of Confidential Access.

II. THE ORANGE BOOK LISTED PATENTS

U.S. PATENT NO.	EXPIRATION DATE
8,129,431	September 11, 2025
8,669,290	January 16, 2024
8,754,131	January 16, 2024
8,871,813	January 16, 2024
8,927,606	January 16, 1024

III. APPLICABLE LEGAL STANDARDS

A. Infringement

Direct infringement occurs when a person or entity makes, uses, offers to sell or sells in the United States a product that is covered by an unexpired patent without the authorization of the patent owner. 35 U.S.C. §271(a).

The courts have held that all infringement analysis involves two steps. The first step involves interpreting the claims to determine their meaning and scope. *North Am. Vaccine, Inc. v. Am. Cyanamid Co.*, 7 F.3d 1571, 1574 (Fed. Cir. 1993), *cert. denied,* 511 U.S. 1069 (1994). The Supreme Court has held that this first step – claim interpretation – is an issue of law exclusively within the province of the court. *Markman v. Westview Instruments, Inc.*, 517 U.S. 370 (1996). Proper claim interpretation involves consideration of the claim itself, the specification, other claims, the prosecution history and extrinsic evidence, if necessary. *See Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 979-80 (Fed. Cir. 1995), (*en banc*) *aff'd*, 517 U.S. 370 (1996).

The second step involves comparing the properly construed claims to the accused product or process to determine whether the properly construed claims "read on" the accused subject matter. *North Am. Vaccine*, 7 F.3d at 1574. This second step is a factual determination. *Hormone Research Found., Inc. v. Genentech, Inc.*, 904 F.2d 1558, 1562 (Fed. Cir. 1990), *cert. dismissed*, 499 U.S. 955 (1991). The Federal Circuit has explained that "[i]n order for there to be infringement, each and every limitation set forth in a patent claim must be found in the accused product, either literally or under the doctrine of equivalents." *CVI/Beta Ventures, Inc. v. Tura LP*, 112 F.3d 1146, 1161 (Fed. Cir. 1997); *see also Tanabe Seiyaku Co., Ltd., v. United States Int'l Trade Comm'n*, 109 F.3d 726, 731 (Fed. Cir. 1997), *cert. denied*, 522 U.S. 1027 (1997) ("The patent owner must show that every limitation of the patent claim asserted is found in the accused process or product, either literally or under the doctrine of equivalents.").

The patent owner bears the burden to prove infringement by a preponderance of the evidence. *Id.* at 731. This standard applies to both literal infringement and infringement under the doctrine of equivalents. *Lemelson v. United States*, 752 F.2d 1538, 1547 (Fed. Cir. 1985). The burden to prove infringement rests at all times on the patent owner and must be established by accurate, scientific methods. *Novartis Corp. v. Ben Venue Labs., Inc.*, 271 F.3d 1043, 1050 (Fed. Cir. 2001).

1. Claim Construction

The courts construe the claims of each patent according to the hierarchy of evidence articulated in *Markman*, looking first to the intrinsic evidence of the patent. *Markman,* 52 F.3d at 979, quoting *Unique Concepts, Inc. v. Brown,* 939 F.2d 1558, 1561 (Fed. Cir. 1991) ("To ascertain the meaning of claims, we consider three sources: The claims, the specification, and the prosecution history.") The court begins with the language of the disputed claims, which define the scope of the invention and the rights of the patentee. *Markman*, 517 U.S. at 373-74; *Phillips v. AWH Corp.*, 415 F.3d 1303, 1314 (Fed. Cir. 2005) (*en banc*), *cert. denied*, 126 S.Ct.

1332 (Feb. 21, 2006). The court may consider not only the language of the disputed claims themselves, but also the language of the unasserted claims. *Phillips*, 415 F.3d at 1314-15. Claims should be construed as they would be by a person of ordinary skill in the art. *Phillips*, 415 F.3d at 1313-14; *Ekchian v. Home Depot, Inc.*, 104 F.3d 1299, 1302 (Fed. Cir. 1997). Moreover, the court must construe the words of the claim as of the time of the invention or when the application was first filed. *Phillips*, 415 F.3d 1313; *Leggett & Platt, Inc. v. Hickory Springs Mfg. Co.*, 285 F.3d 1353, 1357 (Fed. Cir. 2002). Thus, the focus in construing disputed claim terms is not the subjective intent of the inventor or examiner; rather, it is the objective test of what one of ordinary skill in the art at the time of the invention would have understood a claim term to mean. *See Markman*, 52 F.3d at 986; *Phillips*, 415 F.3d at 1313.

Each and every word in a claim must be construed to have meaning. *Exxon Chem. Patents, Inc. v. Lubrizol Corp.*, 64 F.3d 1553, 1557 (Fed. Cir. 1995). Claim terms generally are given their ordinary and customary meaning as of the date of the application for the patent. *Phillips*, 415 F.3d at 1313; *Kopykake Enters., Inc. v. Lucks Co.*, 264 F.3d 1377, 1383 (Fed. Cir. 2001). They also must "be read in accordance with the precepts of English grammar." *In re Hyatt*, 708 F.2d 712, 714 (Fed. Cir. 1983). This strong presumption "in favor of the ordinary meaning of claim language as understood by one of ordinary skill in the art" may be overcome where: 1) the patentee has chosen to become his or her own lexicographer by clearly and explicitly defining the claim term; or 2) a claim term would "deprive[] the claim of clarity such that there is 'no means by which the scope of the claim may be ascertained from the language used.'" *Bell Atl. Network Servs., Inc. v. Covad Comms. Group, Inc.*, 262 F.3d 1258, 1268 (Fed. Cir. 2001) (internal citations omitted). When a patentee chooses to be his or her own lexicographer and uses terms in a manner other than their ordinary meaning, the intended definition of the term must be "clearly stated in the patent specification or file history." *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir 1996); *see also Novo Nordisk of N. Am., Inc. v. Genentech, Inc.*, 77 F.3d 1364, 1368 (Fed. Cir. 1996); *Intellicall, Inc. v. Phonometrics, Inc.*, 952 F.2d 1384, 1387 (Fed. Cir. 1992).

The court should look to the specification and the file history to see if the inventor varied the ordinary meaning of particular claim terms or if a claim term is unclear. *Phillips*, 415 at 1315, 1317; *Phonometrics, Inc. v. N. Telecom Inc.*, 133 F.3d 1459, 1466 (Fed. Cir. 1998). Specifications can be "the single best guide to the meaning of a disputed term" and, therefore, are always "highly relevant to the claim construction analysis." *Phillips*, 415 F.3d at 1315. A patentee need not deliberately or precisely define a term in a lexicographical manner, but may provide a definition by implication. *Vitronics*, 90 F.3d at 1582. Thus, the Federal Circuit has "specifically held that the written description of the preferred embodiments 'can provide guidance as to the meaning of the claims'" that are to be construed, "even if the guidance is not provided in explicit definitional format." *Bell Atl. Network*, 262 F.3d at 1268 (quoting *SciMed Life Sys., Inc. v. Advanced Cardiovascular Sys., Inc.*, 242 F.3d 1337, 1344 (Fed. Cir. 2001)).

The prosecution history of a patent ordinarily should be considered during a claim construction analysis. *Markman*, 52 F.3d at 980 ("The court has broad power to look as a matter of law to the prosecution history of the patent in order to ascertain the true meaning of language used in the patent claims..."). The prosecution history is intrinsic evidence and is "often of critical significance in determining the meaning of the claims." *Vitronics*, 90 F.3d at

1582; *Phillips*, 415 F.3d 1317. In addition, prior art considered by the United States Patent and Trademark Office ("USPTO") during prosecution of a patent comprises intrinsic evidence for claim construction. *Vitronics*, 90 F.3d at 1583.

"In most situations, an analysis of the intrinsic evidence alone will resolve any ambiguity in a disputed claim term." *Id.* When the meaning cannot be determined by intrinsic evidence, a court may turn to extrinsic evidence to construe the claims in a patent. *Phillips*, 415 F.3d at 1317-18; *Vitronics*, 90 F.3d at 1584. "Extrinsic evidence consists of all evidence external to the patent and prosecution history, including expert and inventor testimony, dictionaries, and learned treatises" and may be useful to show "the state of the art at the time of the invention." *Markman*, 52 F.3d at 980. "The court may, in its discretion, receive extrinsic evidence in order 'to aid the court in coming to a correct conclusion' as to the 'true meaning of the language employed' in the patent." *Id.* (internal citations omitted); *see also Key Pharms. v. Hercon Labs. Corp.*, 161 F.3d 709, 716 (Fed. Cir. 1998) (holding that a trial court can hear extrinsic evidence to educate itself about patent and relevant technology, but may not use extrinsic evidence to vary or contradict claim terms). When consideration of extrinsic evidence is necessary to understand the meaning of claim terms, the court may consider testimony on how a person skilled in the art would understand technical terms in the claims. *Cybor Corp. v. FAS Techs., Inc.*, 138 F.3d 1448, 1475 (Fed. Cir. 1998) ("The objective of claim interpretation is to discern the meaning of the claim terms to one of ordinary skill in the art at the time of invention.") Where the intrinsic evidence unambiguously describes the scope of the patent, however, it is improper to rely on extrinsic evidence to alter the meaning of the claims. *See Vitronics*, 90 F.3d at 1584. Thus, in most instances, a thorough consideration of the intrinsic evidence alone will resolve any ambiguity in a disputed claim term, and the court may not rely on extrinsic evidence to construe the scope of a claim term unless the court first finds that the term is ambiguous even in light of the intrinsic evidence. *See Id.* at 1583-85.

2. Literal Infringement

To determine literal infringement, the relevant inquiry is whether *all* the elements contained in the claim appear in the product under consideration. A product that has all of the claimed elements is said to be a literal infringement. For open-ended claims, with the word "comprising" in the preamble, it typically does not matter that the product has elements in addition to the ones specified in the claim. The product is said to infringe literally when it has everything mentioned in the claim. *See Litton Sys., Inc. v. Honeywell, Inc.*, 140 F.3d 1449, 1454 (Fed. Cir. 1998) ("Literal infringement requires that the accused device contain each limitation of the claim exactly; any deviation from the claim precludes a finding of literal infringement."); *Kahn v. Gen. Motors Corp.*, 135 F.3d 1472, 1476-77 (Fed. Cir. 1998) ("To establish literal infringement, a plaintiff must demonstrate that every limitation in the claim is literally met by the accused device."). On the other hand, a product that does not have each and every element recited in the claim should not be considered a literal infringement. *Mas-Hamilton Group v. LaGard, Inc.*, 156 F.3d 1206, 1211 (Fed. Cir. 1998).

3. The Doctrine of Equivalents

Even if a device or method does not infringe literally, infringement still can be found under the doctrine of equivalents. *Graver Tank & Mfg. Co. v. Linde Air Prods. Co.*, 339 U.S. 605, 609 (1950). The Supreme Court has confirmed that "the doctrine of equivalents must be applied to individual elements of the claim, not to the invention as a whole." *Warner-Jenkinson Co., Inc. v. Hilton Davis Chem. Co.*, 520 U.S. 17 (1997). Thus, to infringe a claim, each claim element must be present in the accused subject matter literally or by equivalents. *See London v. Carson Pirie Scott & Co.*, 946 F.2d 1534, 1538 (Fed. Cir. 1991); *Dolly Inc. v. Spalding & Evenflo Cos.*, 16 F.3d 394, 397 (Fed. Cir. 1994). Conversely, "[t]here can be no infringement as a matter of law if a claim limitation is totally missing from the accused device." *London*, 946 F.2d at 1539.

The determination of equivalents should be applied as an objective inquiry on an element-by-element basis. *RF Delaware, Inc. v. Pacific Keystone Techs., Inc.*, 326 F.3d 1255, 1266-67 (Fed. Cir. 2003); *Pennwalt Corp. v. Durand-Wayland Inc.*, 833 F.2d 931, 935 (Fed. Cir. 1987) (*en banc*) (overruled on other grounds) (infringement under the doctrine of equivalents requires the presence of the equivalent of each claim element or limitation). The Supreme Court has left it to the Federal Circuit to refine the formulation of the test for equivalents on a case by case basis. In *Hilton Davis Chem. Co. v. Warner-Jenkinson Co.*, 62 F.3d 1512, 1518 (Fed. Cir. 1995) (*en banc*), *rev'd on other grounds*, 520 U.S. 17 (1997), the Federal Circuit held that "application of the doctrine of equivalents rests on the substantiality of the differences between the claimed and accused products or processes, assessed according to an objective standard." One way of determining "substantiality" under the doctrine of equivalents is if the accused product or process performs substantially the same function, in substantially the same way, to achieve substantially the same results as the claims. *See id., see also Goodwall Constr. Co. v. Beers Constr. Co.*, 991 F.2d 751, 757-58 (Fed. Cir. 1993).

Several principles restrict the applicability of the doctrine of equivalents. One such restriction is the doctrine of claim vitiation. The doctrine of claim vitiation applies when a patentee attempts to argue that the doctrine of equivalents can be used to entirely eliminate a claim element. If the patentee argues that the allegedly infringing product infringes a claim under the doctrine of equivalents because it accomplishes the same results in the same manner, but does not prove the existence of an equivalent for each and every claim element, then the patentee has violated the doctrine of claim vitiation. The United States Supreme Court has stated: "[i]t is important to ensure that the application of the doctrine [of equivalents], even as to an individual element, is not allowed such broad play as to effectively eliminate that element in its entirety." *Warner-Jenkinson,* 520 U.S. at 29. Thus, "the 'all elements rule' provides that the doctrine of equivalents does not apply if applying the doctrine would vitiate an entire claim limitation." *Asyst Techs., Inc. v. Emtrak, Inc.*, 402 F.3d 1188, 1195 (Fed. Cir. 2005).

B. Validity

Under 35 U.S.C. §282, patents are presumed valid and a party asserting invalidity must overcome this presumption by clear and convincing evidence establishing facts which support the conclusion of invalidity. *Texas Instruments Inc. v. U.S. Int'l Trade Comm'n*, 988 F.2d 1165, 1177 (Fed. Cir. 1993). Once a challenger has presented a *prima facie* case of invalidity, the burden shifts to the patentee to go forward with rebuttal evidence. *See Mas-Hamilton Group v. LaGard, Inc.*, 156 F.3d 1206, 1216 (Fed. Cir. 1998).

1. Obviousness

Under 35 U.S.C. § 103(a), a patent claim is obvious, and therefore invalid, "if the differences between the subject matter . . . patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." A party challenging the validity of a claim under § 103 must "prove by clear and convincing evidence that the claimed invention would have been obvious in view of the prior art." *Kahn v. General Motors Corp.*, 135 F.3d 1472, 1479-80 (Fed. Cir. 1998); *Sciele Pharma Inc. v. Lupin Ltd.*, 684 F.3d 1253 (Fed. Cir. 2012); *i4i Ltd. Partnership v. Microsoft Corp.*, 598 F.3d 831, 848 (Fed. Cir. 2010), *aff'd* 131 S.Ct. 2238 (June 9, 2011).

The obviousness analysis includes an assessment of (1) the level of ordinary skill in the pertinent art, (2) the scope and content of the prior art, (3) the differences between the prior art and the claimed subject matter, and (4) any objective evidence of nonobviousness, often referred to as secondary considerations. *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litigation*, 676 F.3d 1063, 1068-69 (Fed. Cir. 2012); *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17-18 (1966). The "secondary considerations" relating to the obviousness inquiry include commercial success, long felt but unsolved need and failure of others. *Id.*

In order to determine obviousness, a court can look to: 1) "interrelated teachings of multiple patents;" 2) "the effects of demands known to the design community or present in the marketplace;" and 3) "the background knowledge possessed by a person having ordinary skill in the art." The determination should be based upon "whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue." *KSR Intern. Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1740-41 (2007). The analysis of obviousness "need not seek out precise teachings directed to the specific subject matter of the challenged claim"–a court can take into account "inferences and creative steps that a person of skill in the art would employ." *Id.* at 1741.

In deciding obviousness, neither the actual motivation nor the purported motivation of the patentee controls. Rather, the objective reach of the claim is what matters. If the claim extends to what is obvious, then it is invalid under § 103. "One of the ways in which a patent's subject matter can be proved obvious is by noting that there existed at the time of invention a

known problem for which there was an obvious solution encompassed by the patent's claims." *Id.* at 1742.

IV. The '431 Patent, Aqueous Liquid Preparation Containing 2-amino-3-(4-bromobenzoyl)phenylacetic Acid

The application that became the '431 patent was filed with the USPTO on March 28, 2005 and assigned Serial No. 10/525,006 ("the '431 patent application"). The '431 patent application was the U.S. national stage entry of International Application No. PCT/JP04/00350, filed January 16, 2004.

The named inventors of the '431 patent are Shirou Sawa and Shuhei Fujita. The '431 patent is assigned on its face to Senju Pharmaceutical Co., Ltd. of Osaka, Japan.

The claims of the '431 patent, which issued on March 6, 2012, are reproduced below:

1. 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, 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.

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 %.

('431 patent.)

V. The '290 Patent, Aqueous Liquid Preparation Containing 2-amino-3-(4-bromobenzoyl)phenylacetic Acid

The 'application that became the '290 Patent was filed with the USPTO on November 28, 2012 and assigned U.S. Patent Application No. 13/687,242 ("the '290 Patent application"). The '290 Patent application was a division of U.S. Patent Application No. 13/353,653, filed January 19, 2012, now U.S. Patent No. 8,497,304 ("the '304 Patent"), which in turn was a division of the '431 patent application, filed March 28, 2005, now the '431 Patent. The '431 Patent application was the U.S. national stage entry of International Application No. PCT/JP04/00350, filed January 16, 2004.

The named inventors of the '290 Patent are Shirou Sawa and Shuhei Fujita. The '290 Patent is assigned on its face to Senju Pharmaceutical Co., Ltd. of Osaka, Japan.

The '290 Patent issued on March 11, 2014 with thirty claims as follows:

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 %.

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.

('290 Patent.)

VI. The '131 Patent, Aqueous Liquid Preparation Containing 2-amino-3-(4-bromobenzoyl)phenylacetic Acid

The application that became the '131 Patent was filed with the USPTO on January 28, 2014 and assigned U.S. Patent Application No. 14/165,976 ("the '131 Patent application"). The '131 Patent application was described as a division of U.S. Patent Application No. 13/687,242, filed November 28, 2012, now the '290 Patent, which in turn was a division of U.S. Patent Application No. 13/353,653, filed January 19, 2012 and now the '304 Patent. U.S. Patent Application No. 13/353,653 was a division of the '431 Patent application, filed March 28, 2005, now the '431 Patent. The '431 Patent application was the U.S. national stage entry of International Application No. PCT/JP04/00350, filed January 16, 2004.

The named inventors of the '131 Patent are Shirou Sawa and Shuhei Fujita. The '131 Patent is assigned on its face to Senju Pharmaceutical Co., Ltd. of Osaka, Japan.

The '131 Patent issued on June 17, 2014 with thirty claims as follows:

1. A stable aqueous liquid preparation comprising: (a) a first component; and (b) a second component; wherein the first component is 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate; the first component is the sole

pharmaceutical active ingredient contained in the preparation and is present in the preparation at a concentration from about 0.05 w/v% to about 0.2 w/v%; the second component is tyloxapol and is present in said liquid preparation in an amount sufficient to stabilize said first component; and wherein said stable liquid preparation is formulated for ophthalmic administration.

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

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

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

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

6. The stable aqueous liquid preparation of claim 1, wherein the stable aqueous liquid preparation consists essentially of: (a) 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt; (b) tyloxapol; (c) boric acid; (d) sodium tetraborate; (e) EDTA sodium salt; (f) benzalkonium chloride; (g) polyvinylpyrrolidone; and (h) sodium sulfite; and wherein the liquid preparation is formulated for ophthalmic administration, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.02 w/v % to about 0.1 w/v %, and wherein the concentration of tyloxapol is from about 0.01 w/v% to about 0.05 w/v%.

7. A stable aqueous liquid preparation comprising: (a) a first component; and (b) a second component; wherein the first component is 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate; the first component is the sole pharmaceutical active ingredient contained in the preparation and is present in the preparation at a concentration from about 0.05 w/v% to about 0.2 w/v%; the second component is tyloxapol; wherein said stable liquid preparation is formulated for ophthalmic administration; and wherein the stable aqueous liquid preparation is characterized in that greater than about 90%

of the original amount of the first component remains in the preparation after storage at about 60° C for 4 weeks.

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

9. The stable aqueous liquid preparation of claim 7, wherein the stable aqueous liquid preparation is characterized in that greater than about 92% of the original amount of the first component remains in the preparation after storage at about 60° C for 4 weeks.

10. The aqueous liquid preparation according to claim 7, wherein the concentration of tyloxapol is from about 0.01 w/v % to about 0.05 w/v %; and wherein the first component is a 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.05 to about 0.1 w/v %.

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

12. The stable aqueous liquid preparation of claim 7; wherein the stable aqueous liquid preparation consists essentially of: (a) 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate; (b) tyloxapol; (c) boric acid; (d) sodium tetraborate; (e) EDTA sodium salt; (f) benzalkonium chloride; (g) polyvinylpyrrolidone; and (h) sodium sulfite; and wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.05 w/v % to about 0.1 w/v %, and the concentration of tyloxapol is about 0.02 w/v%.

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

include mannitol.

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

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

16. The aqueous liquid preparation according to claim 13, wherein the concentration of tyloxapol is from about 0.01 w/v % to about 0.05 w/v % and the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.05 to about 0.1 w/v %.

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

18. The stable aqueous liquid preparation of claim 13; wherein the stable aqueous liquid preparation consists essentially of: (a) 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate; (b) tyloxapol; (c) boric acid; (d) sodium tetraborate; (e) EDTA sodium salt; (f) benzalkonium chloride; (g) polyvinylpyrrolidone; and (h) sodium sulfite; wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.02 w/v % to about 0.1 w/v %, and the concentration of tyloxapol is from about 0.02 w/v% to about 0.05 w/v%.

19. The stable aqueous liquid preparation of claim 13; wherein the stable aqueous liquid preparation is characterized in that greater than about 90% of the original amount of the first component remains in the preparation after storage at about 60° C for 4 weeks.

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

21. The stable aqueous liquid preparation of claim 19; wherein the stable aqueous liquid preparation is characterized in that greater than about 92% of the original amount of the first component remains in the preparation after storage at about 60° C for 4 weeks.

22. The aqueous liquid preparation according to claim 21, wherein the concentration of tyloxapol is from about 0.01 w/v % to about 0.05 w/v %; and wherein the first component is a 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.05 to about 0.1 w/v %.

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

24. The stable aqueous liquid preparation of claim 13; wherein the stable aqueous liquid preparation consists essentially of: (a) 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate; (b) tyloxapol; (c) boric acid; (d) sodium tetraborate; (e) EDTA sodium salt; (f) benzalkonium chloride; (g) polyvinylpyrrolidone; and (h) sodium sulfite; wherein said liquid preparation is formulated for ophthalmic administration; and wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.05 w/v % to about 0.1 w/v %.

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

26. The aqueous liquid preparation of claim 4, wherein the aqueous liquid preparation further satisfies the preservative efficacy standard of US Pharmacopoeia as follows:
viable cell counts of bacteria (*S. aureus, P. aeruginosa*) 24 hours and 7 days after inoculation decrease to not more than 1/10 and not more than 1/1000, respectively, and thereafter, the cell count levels off or decreases; and
viable cell count of fungi (*C. albicans, A. niger*) 14 days after inoculation decreases to not more than 1/10, and thereafter, the cell count keeps the same level as that of 14 days after inoculation.

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

28. The aqueous liquid preparation of claim 9, wherein the aqueous liquid preparation further satisfies the preservative efficacy standard of US Pharmacopoeia as follows:
viable cell counts of bacteria (*S. aureus, P. aeruginosa*) 24 hours and 7 days after inoculation decrease to not more than 1/10 and not more than 1/1000, respectively, and thereafter, the cell count levels off or decreases; and
viable cell count of fungi (*C. albicans, A. niger*) 14 days after inoculation decreases to not more than 1/10, and thereafter, the cell count keeps the same level as that of 14 days after inoculation.

29. The aqueous liquid preparation of claim 13, wherein the aqueous liquid preparation further satisfies the preservative efficacy standard of US Pharmacopoeia as follows:
viable cell counts of bacteria (*S. aureus, P. aeruginosa*) 24 hours and 7 days after inoculation decrease to not more than 1/10 and not more than 1/1000, respectively, and thereafter, the cell count levels off or decreases; and
viable cell count of fungi (*C. albicans, A. niger*) 14 days after inoculation decreases to not more than 1/10, and thereafter, the cell count keeps the same level as that of 14 days after inoculation.

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

('131 Patent.)

VII. The '813 Patent, Aqueous Liquid Preparation Containing 2-amino-3-(4-bromobenzoyl)phenylacetic Acid

The application that became the '813 patent was filed with the USPTO on April 25, 2014 and assigned U.S. Patent Application No. 14/261,720 ("the '813 patent application"). The '813 patent application was described as a division of U.S. Patent Application No. 14/165,976, filed January 28, 2014, now the '131 patent. The '131 patent application was described as a division of U.S. Patent Application No. 13/687,242, filed November 28, 2012, now the '290 patent, which in turn was described as a division of U.S. Patent Application No. 13/353,653, filed January 19, 2012 and now the '304 patent. U.S. Patent Application No. 13/353,653 was described as a division of U.S. Patent Application No. 10/525,006, filed March 28, 2005, now the '431 patent. The '431 patent application was the U.S. national stage entry of International Application No. PCT/JP04/00350, filed January 16, 2004.

The named inventors of the '813 patent are Shirou Sawa and Shuhei Fujita. The '813 patent is assigned on its face to Senju Pharmaceutical Co., Ltd. of Osaka, Japan.

The '813 patent issued on October 28, 2014 with twenty-seven claims as follows:

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

2. The aqueous liquid preparation according to claim 1, wherein the aqueous liquid preparation further consists of sodium sulfite.

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

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

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

about 8.5.

6. The stable aqueous liquid preparation of claim 1; wherein the stable aqueous liquid preparation consists of: (a) 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt; (b) tyloxapol; (c) boric acid; (d) sodium tetraborate; (e) EDTA sodium salt; (f) polyvinylpyrrolidone; (g) sodium sulfite; and (h) water; wherein said liquid preparation is formulated for ophthalmic administration, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.02 w/v % to about 0.1 w/v %, and wherein the concentration of tyloxapol is from about 0.01 w/v % to about 0.05 w/v %.

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

8. The aqueous liquid preparation according to claim 7, wherein the aqueous liquid preparation further consists of sodium sulfite.

9. The stable aqueous liquid preparation of claim 7; wherein the stable aqueous liquid preparation is characterized in that greater than about 92% of the original amount of the first component remains in the preparation after storage at about 60° C. for 4 weeks.

10. The aqueous liquid preparation according to claim 7; wherein the concentration of tyloxapol is from about 0.01 w/v % to about 0.05 w/v %; and wherein the first component is a 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.05 w/v % to about 0.1 w/v %.

11. The aqueous liquid preparation according to claim 10, wherein

the pH is from about 7.5 to about 8.5.

12. The stable aqueous liquid preparation of claim 7; wherein the stable aqueous liquid preparation consists 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) polyvinylpyrrolidone; (g) sodium sulfite; and (h) water; and wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.05 w/v % to about 0.1 w/v %, and the concentration of tyloxapol is about 0.02 w/v %.

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

14. The aqueous liquid preparation according to claim 13, wherein the aqueous liquid preparation further consists of sodium sulfite.

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

16. The aqueous liquid preparation according to claim 13, wherein the concentration of tyloxapol is from about 0.01 w/v % to about 0.05 w/v % and the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.05 to about 0.1 w/v %.

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

18. The stable aqueous liquid preparation of claim 13; wherein the stable aqueous liquid preparation consists 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) polyvinylpyrrolidone; (g) sodium sulfite; and (h) water; wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.02 w/v % to about 0.1 w/v %, and the concentration of tyloxapol is from about 0.02 w/v % to about 0.05 w/v %.

19. The stable aqueous liquid preparation of claim 13; wherein the stable aqueous liquid preparation is characterized in that greater than about 90% of the original amount of the first component remains in the preparation after storage at about 60° C. for 4 weeks.

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

21. The stable 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 0.05 w/v % to about 0.1 w/v %.

22. The aqueous liquid preparation according to claim 21, wherein the pH of the aqueous liquid preparation is from about 7.5 to about 8.5.

23. The stable aqueous liquid preparation of claim 13; wherein the stable aqueous liquid preparation consists 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) polyvinylpyrrolidone; (g) sodium sulfite; and (h) water; wherein said liquid preparation is formulated for ophthalmic administration; and wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.05 w/v % to about 0.1 w/v %.

24. The aqueous liquid preparation of claim 1, wherein the aqueous liquid preparation does not include any preservative.

25. The aqueous liquid preparation of claim 7, wherein the aqueous liquid preparation does not include any preservative.

26. The aqueous liquid preparation of claim 13, wherein the aqueous liquid preparation does not include any preservative.

27. The aqueous liquid preparation according to claim 1, optionally further consisting of one or more additives selected from the group consisting of buffers, thickeners, stabilizers, chelating agents, and pH controlling agents.

('813 patent)

VIII. The '606 Patent, Aqueous Liquid Preparation Containing 2-amino-3-(4-bromobenzoyl)phenylacetic Acid

The application that became the '606 patent was filed with the USPTO on September 23, 2014 and assigned U.S. Patent Application No. 14/493,903 ("the '606 patent application"). The '606 patent application is described as a division of the '813 patent application, filed April 25, 2014 and now the '813 patent. The '813 patent application was described as a division of the '131 patent application, filed January 28, 2014, now the '131 patent. The '131 patent application was described as a division of the '290 patent application, filed November 28, 2012, now the '290 patent, which in turn was described as a division of the '304 patent application, filed January 19, 2012, now the '304 patent. The '304 patent application was described as a division of the '431 patent application, filed March 28, 2005, now the '431 patent. The '431 patent application was the U.S. national stage entry of International Application No. PCT/JP04/00350, filed January 16, 2004.

The named inventors of the '606 patent are Shirou Sawa and Shuhei Fujita. The '606 patent is assigned on its face to Senju Pharmaceutical Co., Ltd. of Osaka, Japan.

The '606 patent issued on January 6, 2015 with thirty claims as follows:

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

sufficient to stabilize said first component; wherein said stable liquid preparation is formulated for ophthalmic administration; and wherein said liquid preparation is administered to said eye at a dose and a frequency effective to treat said inflammatory disease.

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

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

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

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

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

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

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

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

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

11. A method for treating an inflammatory disease of an eye, the method comprising administering to said eye a stable aqueous liquid preparation that comprises: (a) a first component; and (b) a second component; wherein the first component is 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate; the first component is the sole pharmaceutical active ingredient contained in the preparation; the second component is tyloxapol; wherein said stable liquid preparation is formulated for ophthalmic administration; wherein the stable aqueous liquid preparation is characterized in that greater than about 90% of the original amount of the first component remains in the preparation after storage at about 60° C. for 4 weeks; and wherein said liquid preparation is administered to said eye at a dose and a frequency effective to treat said inflammatory disease.

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

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

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

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

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

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

18. The method according to claim 11, wherein the stable aqueous

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

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

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

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

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

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

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

25. The method according to claim 20; wherein the stable aqueous liquid preparation consists essentially of: (a) 2-amino-3-(4-

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

26. The method according to claim 20, wherein the stable aqueous liquid preparation is characterized in that greater than about 90% of the original amount of the first component remains in the preparation after storage at about 60° C. for 4 weeks.

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

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

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

30. The method according to claim 19, wherein the aqueous liquid preparation further satisfies the preservative efficacy standard of EP-criteria B of the European Pharmacopoeia as follows: viable

cell counts of bacteria (*S. aureus, P. aeruginosa*) 24 hours and 7 days after inoculation decrease to not more than 1/10 and not more than 1/1000, respectively, and thereafter, the cell count levels off or decreases; and viable cell count of fungi (*C. albicans, A. niger*) 14 days after inoculation decreases to not more than 1/10, and thereafter, the cell count keeps the same level as that of 14 days after inoculation.

('606 patent.)

IX. Non-Infringement

A. Claim Construction

The terms in the claims of the '431, '290, '131, '813 and '606 patents should be accorded their normal meaning in the art, as informed by the specification and prosecution history.

B. The '431 Patent

1. The Watson ANDA Product Does Not Infringe Claims 5 And 22 Of The '431 Patent Because The Watson ANDA Product Does Not Contain The Claimed Amount Of Bromfenac Sodium

Claim 5 of the '431 Patent depends from claim 4, which in turn depends from claim 3, which depends from independent claim 1. Claims 1, 3, 4 and 5 of the '431 Patent read as follows:

1. 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, 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.

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 %.

('431 Patent at col.11, l.66 to col.12, l.31.)

Claim 5 requires that bromfenac sodium be present in an amount of "about 0.1 w/v %." The Watson ANDA Product does not contain "about 0.1 w/v %" of bromfenac sodium. Therefore, the Watson ANDA product does not literally infringe claim 5 of the '431 Patent.

Claim 5 of the '431 Patent cannot be expanded under the doctrine of equivalents to encompass the Watson ANDA product based upon claim vitiation. That is, if claim 5 of the '431 Patent was expanded to include the Watson ANDA product, which does not contain "about 0.1 w/v %" of bromfenac sodium, then the entire claim element of requiring "about 0.1 w/v %" of bromfenac sodium would be vitiated. Such an interpretation under the doctrine of equivalents is improper. *See Asyst Techs., Inc.*, 402 F.3d at 1195; *Freedman Seating Co.*, 420 F.3d at 1358.

Claim 22 of the '431 Patent depends from claim 20, which in turn depends from claim 19, which depends from independent claim 18. Claims 18-20 and 22 of the '431 Patent read as follows:

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 %.

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 %.

('431 Patent at col.13, l.16 to col.14, l.22.)

Claim 22 requires that bromfenac sodium be present in an amount of "about 0.1 w/v %." The Watson ANDA Product does not contain "about 0.1 w/v %" of bromfenac sodium. Therefore, the Watson ANDA product does not literally infringe claim 22 of the '431 Patent.

Claim 22 of the '431 Patent cannot be expanded under the doctrine of equivalents to encompass the Watson ANDA product based upon claim vitiation. That is, if claim 22 of the '431 Patent was expanded to include the Watson ANDA product, which does not contain "about 0.1 w/v %" of bromfenac sodium, then the entire claim element of requiring "about 0.1 w/v %" of bromfenac sodium would be vitiated. Such an interpretation under the doctrine of equivalents is improper. *See Asyst Techs., Inc.*, 402 F.3d at 1195; *Freedman Seating Co.*, 420 F.3d at 1358.

2. The Watson ANDA Product Does Not Infringe Claims 11 And 15-17 Of The '431 Patent Because The Watson ANDA Product Does Not Contain The Claimed Amount Of Bromfenac Sodium

Claim 11 of the '431 Patent depends from claim 4, which in turn depends from claim 3, which depends from independent claim 1. Claims 1, 3, 4 and 11 of the '431 Patent read as follows:

1. 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, 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.

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 %.

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 %.

('431 Patent at col.11, l.66 to col.12, l.51.)

Claim 11 requires that bromfenac sodium be present in an amount of "about 0.2 w/v %." The Watson ANDA product does not contain "about 0.2 w/v %" of bromfenac sodium, Therefore, the Watson ANDA product does not literally infringe claim 11 of the '431 Patent.

Claim 11 of the '431 Patent cannot be expanded under the doctrine of equivalents to encompass the Watson ANDA product based upon claim vitiation. That is, if claim 11 of the '431 Patent were expanded to include the Watson ANDA product, which does not contain "about 0.2 w/v %" of bromfenac sodium, then the entire claim element requiring "about 0.2 w/v %" of bromfenac sodium would be vitiated. Such an interpretation under the doctrine of equivalents is improper. *See Asyst Techs., Inc.*, 402 F.3d at 1195; *Freedman Seating Co.*, 420 F.3d at 1358.

Claims 15-17 depend either directly or indirectly from claim 11 of the '431 Patent and thereby incorporate all the limitations of claim 11. *See* 35 U.S.C. § 112, ¶ 4 (providing in relevant part "A claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers."). Therefore, the Watson ANDA product does not infringe claims 15-17 of the '431 Patent either literally or under the doctrine of equivalents for the reasons discussed above regarding claim 11 of the '431 Patent. *See Wolverine World Wide, Inc. v. Nike, Inc.*, 38 F.3d 1192, 1199 (Fed. Cir. 1994) ("It is axiomatic that dependent claims cannot be found infringed unless the claims from which they depend have been found to have been infringed." (internal citations and quotations omitted)).

3. The Watson ANDA Product Does Not Infringe Claim 21 Of The '431 Patent Because The Watson ANDA Product Does Not Contain The Claimed Amount Of Bromfenac Sodium

Claim 21 of the '431 Patent depends from claim 20, which in turn depends from claim 19, which depends from independent claim 18. Claims 18-21 of the '431 Patent read as follows:

> 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 %.

('431 Patent at col.13, l.16 to col.14, l.19.)

Claim 21 requires that bromfenac sodium be present in an amount of "about 0.01 w/v %." The Watson ANDA product does not contain "about 0.01 w/v %" of bromfenac sodium. Therefore, the Watson ANDA product does not literally infringe claim 21 of the '431 Patent.

Claim 21 of the '431 Patent cannot be expanded under the doctrine of equivalents to encompass the Watson ANDA product based upon claim vitiation. That is, if claim 21 of the

'431 Patent were expanded to include the Watson ANDA product, which does not contain "about 0.01 w/v %" of bromfenac sodium, then the entire claim element requiring "about 0.01 w/v %" of bromfenac sodium would be vitiated. Such an interpretation under the doctrine of equivalents is improper. *See Asyst Techs., Inc.*, 402 F.3d at 1195; *Freedman Seating Co.*, 420 F.3d at 1358.

4. The Watson ANDA Product Does Not Infringe Claims 12-14 Of The '431 Patent Because The Watson ANDA Product Does Not Contain The Claimed Amount Of Tyloxapol

Claim 12 of the '431 Patent depends from claim 4, which in turn depends from claim 3, which depends from independent claim 1. Claims 1, 3, 4 and 12 of the '431 Patent read as follows:

> 1. 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, 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.
>
> 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 %.
>
> 12. The aqueous liquid preparation according to claim 4, wherein the concentration of the tyloxapol is about 0.3 w/v %.

('431 Patent at col.11, l.66 to col.12, l.55.)

Claim 12 requires that tyloxapol be present in an amount of "about 0.3 w/v %." The Watson ANDA product does not contain "about 0.3 w/v %" of tyloxapol. Therefore, the Watson ANDA product does not literally infringe claim 12 of the '431 Patent.

Claim 12 of the '431 Patent cannot be expanded under the doctrine of equivalents to encompass the Watson ANDA product based upon claim vitiation. That is, if claim 12 of the '431 Patent were expanded to include the Watson ANDA product, which does not contain "about 0.3 w/v %" of tyloxapol, then the entire claim element requiring "about 0.3 w/v %" of tyloxapol would be vitiated. Such an interpretation under the doctrine of equivalents is improper. *See Asyst Techs., Inc.*, 402 F.3d at 1195; *Freedman Seating Co.*, 420 F.3d at 1358.

Claims 13 and 14 depend from claim 12 of the '431 Patent and thereby incorporate all the limitations of claim 12. *See* 35 U.S.C. § 112, ¶ 4. Therefore, the Watson ANDA product does not infringe claims 13 and 14 of the '431 Patent either literally or under the doctrine of equivalents for the reasons discussed above regarding claim 12 of the '431 Patent. *See Wolverine*, 38 F.3d at 1199.

5. The Watson ANDA Product Does Not Infringe Claims 1-4, 6-10 and 18-20 Of The '431 Patent

Claims 1-4, 6-10 and 18-20 of the '431 patent are not infringed by the Watson ANDA product because the claims of the '431 patent are invalid. "It is axiomatic that one cannot infringe an invalid patent." *Richdel, Inc. v. Sunspool Corp.*, 714 F.2d 1573, 1580 (Fed. Cir. 1983).

C. The '290 Patent

1. The Watson ANDA Product Does Not Infringe Claim 5 Of The '290 Patent Because The Watson ANDA Product Does Not Contain The Claimed Amount Of Bromfenac Sodium

Claim 5 of the '290 patent depends from claim 4 which in turn depends from independent claim 1. Claims 1, 4 and 5 of the '290 Patent read as follows:

> 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.

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 %.

('290 Patent, at col.12, ll.2-28.)

Claim 5 requires that bromfenac sodium be present in an amount of "about 0.1 w/v %." The Watson ANDA product does not contain "about 0.1 w/v %" of bromfenac sodium. Therefore, the Watson ANDA product does not literally infringe claim 5 of the '290 Patent.

Claim 5 of the '290 Patent cannot be expanded under the doctrine of equivalents to encompass the Watson ANDA product based upon claim vitiation. That is, if claim 5 of the '290 Patent were expanded to include the Watson ANDA product, which does not contain "about 0.1 w/v %" of bromfenac sodium, then the claim element requiring "about 0.1 w/v %" of bromfenac sodium would be vitiated. Such an interpretation under the doctrine of equivalents is improper. *See Asyst Techs., Inc.*, 402 F.3d at 1195; *Freedman Seating Co.*, 420 F.3d at 1358.

2. The Watson ANDA Product Does Not Infringe Claims 1-4 and 6-30 Of The '290 Patent

Claims 1-4 and 6-30 of the '290 patent are not infringed by the Watson ANDA product because the claims of the '290 patent are invalid. "It is axiomatic that one cannot infringe an invalid patent." *Richdel, Inc. v. Sunspool Corp.*, 714 F.2d 1573, 1580 (Fed. Cir. 1983)

D. The '131 Patent

1. The Watson ANDA Product Does Not Infringe Claims 1-30 Of The '131 Patent

Claims 1-30 of the '131 patent are not infringed by the Watson ANDA product because the claims of the '131 patent are invalid. "It is axiomatic that one cannot infringe an invalid patent." *Richdel, Inc. v. Sunspool Corp.*, 714 F.2d 1573, 1580 (Fed. Cir. 1983).

E. The '813 Patent

1. The Watson ANDA Product Does Not Infringe Claims 6 and 24 Of The '813 Patent Because the Watson ANDA Product Contains Benzalkonium Chloride

Claims 6 and 24 of the '813 patent are dependent claims that depend from claim 1. Claims 1, 6 and 24 of the '813 patent read as follows:

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

6. The stable aqueous liquid preparation of claim 1; wherein the stable aqueous liquid preparation consists of: (a) 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt; (b) tyloxapol; (c) boric acid; (d) sodium tetraborate; (e) EDTA sodium salt; (f) polyvinylpyrrolidone; (g) sodium sulfite; and (h) water; wherein said liquid preparation is formulated for ophthalmic administration, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.02 w/v % to about 0.1 w/v %, and wherein the concentration of tyloxapol is from about 0.01 w/v % to about 0.05 w/v %.

24. The aqueous liquid preparation of claim 1, wherein the aqueous liquid preparation does not include any preservative.

The Watson ANDA product does not literally infringe claims 6 or 24 of the '813 patent because the Watson ANDA product contains benzalkonium chloride. Benzalkonium chloride cannot be included as an element of the aqueous liquid preparation of claim 6 because claim 6 employs the transitional phrase "consists of," which signifies restriction of the claim to only the recited elements. *Vehicular Techs. Corp. v. Titan Wheel Int'l., Inc.*, 212 F.3d 1377, 1382-83 (Fed. Cir. 2000). Therefore, claim 6 is restricted to the recited elements of 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt, tyloxapol, boric acid, sodium tetraborate, EDTA sodium salt, polyvinylpyrrolidone, sodium sulfite and water.

Preparations containing benzalkonium chloride, a common preservative, are also not within the scope of claim 24 because claim 24 states that the preparation "does not include any preservative." Because the Watson ANDA product contains benzalkonium chloride, the Watson ANDA product cannot literally infringe claim 24.

Further, claims 6 and 24 of the '813 patent cannot be expanded under the doctrine of equivalents to encompass the Watson product based on claim vitiation. That is, if claims 6 and 24 of the '813 patent were expanded to encompass the Watson ANDA product, which contains

benzalkonium chloride, then the "consists of" transitional phrase would be vitiated from claim 6 and the recitation of "does not contain an preservative" would be vitiated from claim 24. Such an interpretation under the doctrine of equivalents is improper. *See Asyst Techs., Inc.*, 402 F.3d at 1195; *Freedman Seating Co. v. Am. Seating Co.*, 420 F.3d 1350, 1358 (Fed. Cir. 2005).

2. Claims 12 and 25

Claims 12 and 25 of the '813 patent are dependent claims that depend from claim 7. Claims 7, 12 and 25 of the '813 patent read as follows:

> 7. A stable aqueous liquid preparation consisting essentially of: (a) a first component; (b) a second component; wherein the first component is 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof; (c) boric acid; (d) sodium tetraborate; and (e) water; wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate; the first component is the sole pharmaceutical active ingredient contained in the preparation and is present in the preparation at a concentration from about 0.05 w/v % to about 0.2 w/v %; the second component is tyloxapol; wherein said stable liquid preparation is formulated for ophthalmic administration; and wherein the stable aqueous liquid preparation is characterized in that greater than about 90% of the original amount of the first component remains in the preparation after storage at about 60° C. for 4 weeks.
>
> 12. The stable aqueous liquid preparation of claim 7; wherein the stable aqueous liquid preparation consists 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) polyvinylpyrrolidone; (g) sodium sulfite; and (h) water; and wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.05 w/v % to about 0.1 w/v %, and the concentration of tyloxapol is about 0.02 w/v %.
>
> 25. The aqueous liquid preparation of claim 7, wherein the aqueous liquid preparation does not include any preservative.

The Watson ANDA product does not infringe claims 12 and 25 of the '813 patent, either literally or under the doctrine of equivalents, for the same reasons discussed above for claims 6 and 24 of the '813 patent, *i.e.*, these claims exclude preparations that contain benzalkonium chloride, which is present in the Watson ANDA product.

3. Claims 18, 23 and 26

Claims 18, 23 and 26 of the '813 patent are dependent claims that depend from claim 13. Claims 13, 18, 23 and 26 of the '813 patent read as follows:

> 13. A stable aqueous liquid preparation consisting essentially of: (a) a first component; and (b) a second component; wherein the first component is 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof; (c) boric acid; (d) sodium tetraborate; and (e) water; wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate; the first component is the sole pharmaceutical active ingredient contained in the preparation and is present in the preparation at a concentration from about 0.05 w/v % to about 0.2 w/v %; the second component is tyloxapol; wherein said stable liquid preparation is formulated for ophthalmic administration; provided that the liquid preparation does not include mannitol.
>
> 18. The stable aqueous liquid preparation of claim 13; wherein the stable aqueous liquid preparation consists 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) polyvinylpyrrolidone; (g) sodium sulfite; and (h) water; wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.02 w/v % to about 0.1 w/v %, and the concentration of tyloxapol is from about 0.02 w/v % to about 0.05 w/v %.
>
> 23. The stable aqueous liquid preparation of claim 13; wherein the stable aqueous liquid preparation consists 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) polyvinylpyrrolidone; (g) sodium sulfite; and (h) water; wherein said liquid preparation is formulated for ophthalmic administration; and wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.05 w/v % to about 0.1 w/v %.
>
> 26. The aqueous liquid preparation of claim 13, wherein the aqueous liquid preparation does not include any preservative.

The Watson ANDA product does not infringe claims 18, 23 and 26 of the '813 patent, either literally or under the doctrine of equivalents, for the same reasons discussed above for claims 6 and 24 of the '813 patent, *i.e.*, these claims exclude preparations that contain benzalkonium chloride, which is present in the Watson ANDA product.

4. The Watson ANDA Product Does Not Infringe Claims 1-5, 7-11, 13-17, 19-22 and 27 Of The '813 Patent

Claims 1-5, 7-11, 13-17, 19-22, and 27 of the '813 patent are not infringed by the Watson ANDA product because the claims of the '813 patent are invalid. "It is axiomatic that one cannot infringe an invalid patent." *Richdel, Inc. v. Sunspool Corp.*, 714 F.2d 1573, 1580 (Fed. Cir. 1983)

F. The '606 Patent

1. The Watson ANDA Product Does Not Infringe Claim 8 Of The '606 Patent Because The Watson ANDA Product Does Not Contain The Claimed Amount Of Bromfenac Sodium

Claim 8 of the '606 patent depends from claim 5 which in turn depends from independent claim 1. Claims 1, 5, and 8 of the '606 patent read as follows:

> 1. A method for treating an inflammatory disease of an eye, the method comprising administering to said eye a stable aqueous liquid preparation that comprises: (a) a first component; and (b) a second component; wherein the first component is 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate; the first component is the sole pharmaceutical active ingredient contained in the preparation; the second component is tyloxapol and is present in said liquid preparation in an amount sufficient to stabilize said first component; wherein said stable liquid preparation is formulated for ophthalmic administration; and wherein said liquid preparation is administered to said eye at a dose and a frequency effective to treat said inflammatory disease.
>
> 5. The method according to claim 1, wherein the concentration of tyloxapol is from about 0.01 w/v % to about 0.05 w/v %; and wherein the first component is a 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt, wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.01 to about 0.2 w/v %.
>
> 8. The method according to claim 5, wherein the concentration of

the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is about 0.1 w/v %.

('606 patent at col. 11, ll. 17-31, 40-45, and 52-54.)

Claim 8 requires that bromfenac sodium be present in an amount of "about 0.1 w/v %." The Watson ANDA product does not contain "about 0.1 w/v %" of bromfenac sodium. Therefore, the Watson ANDA product does not literally infringe claim 8 of the '606 patent.

Claim 8 of the '606 patent cannot be expanded under the doctrine of equivalents to encompass the Watson ANDA product based upon claim vitiation. That is, if claim 8 of the '606 patent were expanded to include the Watson ANDA product, which does not contain "about 0.1 w/v %" of bromfenac sodium, then the claim element requiring "about 0.1 w/v %" of bromfenac sodium would be vitiated. Such an interpretation under the doctrine of equivalents is improper. *See Asyst Techs., Inc.*, 402 F.3d at 1195; *Freedman Seating Co.*, 420 F.3d at 1358.

X. Invalidity

A. Level of Ordinary Skill in the Art

The subject matter of the '431, '290, '131, '813 and '606 patents fall within the chemical/pharmaceutical arts. The level of skill in the art is relatively high, with practitioners having a Ph.D. or other advanced degrees in areas related to chemistry, biology, pharmaceutics or medicine and experience in the field of ophthalmic compositions. *E.I. DuPont de Demours & Co. v. Monsanto*, 903 F. Supp. 680, 751 (D. Del. 1995), *aff'd*, 92 F.3d 1208 (Fed. Cir. 1996). A person of ordinary skill in the art would easily have understood the prior art references referred to herein, and would have the capability to draw inferences from them.

B. Scope and Content of the Prior Art

1. Ogawa et al, U.S. Patent No. 4,910,225, Locally Administrable Therapeutic Composition for Inflammatory Disease

Prior to the earliest filing date of the patents at issue, a person of ordinary skill in the art would have been aware of Ogawa. Ogawa teaches stable ophthalmic compositions containing 0.001% to about 10% w/w % bromfenac sodium, about 0.1 to 10 w/w % of a water-soluble polymer and about 0.1 to 1.0 w/w % of a sulfite with the pH adjusted to 6.0-9.0, preferably 7.5-8.5. (Ogawa at col. 3, line 7 to col. 4, line 45.) Ogawa also teaches the inclusion of benzalkonium chloride and polysorbate 80 in its compositions. (Ogawa at col. 8, line 5 (Experimental Example 4) to col. 11, line 5 (Example 9).)

Ogawa exemplifies the following ophthalmic compositions:

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	

(Ogawa at col. 10, lines 8-17 (Example 6).)

Sodium 3-(4-bromobenzoyl)-2-aminophenyl-acetate monohydrate	0.1 g
Boric acid	1.5 g
Borax	Sufficient quantity
Benzalkonium chloride	0.005 g
Polysorbate 80	0.15 g
Polyvinyl pyrrolidone	2.0 g
Sodium sulfite	0.1 g
Sterile purified water	To make 100 ml
pH 8	

(Ogawa at col. 10, lines 39-49 (Example 8).)

Ogawa also reports the stability of these compositions at 60°C after 4 weeks as follows:

	Appearance	Residue (%)
Example 6	–	100.9
Example 7	–	99.2
Example 8	–	98.9

(Ogawa at col. 14, lines 47-50 and 61-63 (Table 11).)

The sodium 3-(4-bromobenzoyl)-2-aminophenyl-acetate monohydrate employed in Examples 6 and 8 of Ogawa is another name for bromfenac sodium monohydrate. ('431 patent at col. 1, lines 23-53.) The compositions of Examples 6 and 8 are virtually identical to the examples of the patents at issue and the claims of the patents at issue except that polysorbate 80 in Examples 6 and 8 of Ogawa is replaced with tyloxapol.

The other examples of Ogawa disclose and teach a skilled artisan how to vary the composition of a bromfenac solution to improve stability. For example, Experimental Example 4 of Ogawa teaches the following composition:

Formula	
Compound [I]	0.1 g
Borax	1.0 g
Sodium borate	Sufficient quantity
Sodium chloride	0.25 g
Disodium edetate	0.02 g
Benzalkonium chloride	0.005 g
Polysorbate 80	0.3 g
Sterile purified water	To make 100 ml

(Ogawa at col. 8, lines 5-14 (Experimental Example 4).)

Ogawa further reports the stability of the above composition when the pH is varied from 6 to 9 as follows:

	Formula	pH	Appearance	Residue (%)
	-3	pH 8.0	–	98.6
	-4	pH 9.0	–	99.4
3 Weeks	A-1	ph 6.0	+	19.3
	-2	pH 7.0	+	54.2
	-3	pH 8.0	–	98.0
	-4	pH 9.0	–	99.0

Note: The symbol "–" denotes that change in appearance was not observed.
The symbol "+" denotes that change in appearance was observed.
(hereinafter, the same as above)

(Ogawa at col. 14, lines 22-32 (Table 8).) This data demonstrates that the pH of the bromfenac solution is critical to the stability of the solution.

Experimental Example 5 of Ogawa discloses the following compositions:

Formulas	B-1	B-2
Compound [I]	0.1 g	0.1 g
Boric acid	1.5 g	1.5 g
Borax	Sufficient quantity	
Disodium edetate	0.02 g	0.02 g
Benzalkonium chloride	0.007 g	0.007 g
Polysorbate 80	0.15 g	0.15 g
Polyvinyl pyrrolidone	2.0 g	—
Sterile purified water	To make 100 ml	
	pH 8	pH 8

(Ogawa at col. 8, lines 29-39 (Experimental Example 5). Ogawa does not report the residue percentage of bromfenac for Formulas B-1 and B-2, but does report that after storage for four weeks Formula B-1, which contained povidone, did not change its visual appearance while Formula B-2, which did not contain povidone, did change its visual appearance.

Experimental Example 6 of Ogawa teaches Formulas B and B-3 as follows:

Formulas	B	B-3
Compound [I]	0.1 g	0.1 g
Boric acid	1.5 g	1.5 g
Borax	Sufficient quantity	
Disodium edetate	0.02 g	0.02 g
Benzalkonium chloride	0.007 g	0.007 g
Polyvinyl pyrrolidone	0.15 g	0.15 g
Sodium sulfite	—	0.2 g
Sterile purified water	To make 100 ml	
	pH 8	pH 8

(Ogawa at col. 8, lines 51-62 (Experimental Example 6).

Ogawa reports the stability of Formulas B and B-3 as follows:

Formula	Residue (%)	Appearance
B-1	93.4	+
B-3	100.9	–

(Ogawa at col. 14, lines 40-44 (Table 10).[1] The data for Experimental Example 6 confirms that the presence of sodium sulfite enhances the stability of bromfenac sodium aqueous solutions.

Ogawa also teaches the following treatment regimen:

> The ophthalmic composition according to this invention is prepared by incorporating the active compound in a base or vehicle for topical application to the eye....The ophthalmic composition of this invention may be administered in accordance with the following schedules. In the form of eye-drops, one to several drops per dose are instilled with a frequency of once to 4 times a day according to the clinical condition. Of course, the dosage may be adjusted according to symptoms. The ophthalmic composition according to this invention can be used topically for the treatment of inflammatory diseases of the eye without causing local irritant effects and produces beneficial effects surpassing those obtained with the conventional drugs of the same type.

(Ogawa at col. 4, ll. 40-59.)

A person skilled in the art, prior to the earliest filing date of the patents at issue, also would have been aware that polysorbate 80 was a non-ionic surfactant and that tyloxapol was also a non-ionic surfactant and that both non-ionic surfactants were used in ophthalmic products. *See, e.g.,* U.S. Patent No. 5,540,930 at col. 4, lines 15-29 ("[u]seful surface active agents include but are not limited to polysorbate 80, tyloxapol, TWEEN 80 (ICI America., Wilmington, Del.) PLURONIC F-68 (from BASF, Ludwigshafen, Germany) and the

[1] Table 10 contains a typographical error and refers to Formula B as B-1.

poloxamer"); U.S. Patent No. 5,597,560 at col. 4, lines 24-31; U.S. Patent No. 5,603,929 at col. 3, lines 37-41.[2]

2. Kapin et al., International Publication No. WO 02/13804, Method of Treating Angiogenesis-Related Disorders Using Benzoyl Phenylacetetic Acid

A person skilled in the art, prior to the earliest filing date of the patents at issue, also would have been aware of Kapin. Kapin teaches ophthalmic compositions comprising 3-benzoylphenlacetic acids and exemplifies the following composition:

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%

(Kapin at p. 7, lines 15-22.)

In the background section, Kapin describes the prior art as follows:

> U.S. Patent No. 4,910,225 [Ogawa] teaches certain benzoylphenylacetic acids for local administration to control ophthalmic, nasal or otic inflammation. Only acetic acids are disclosed in the '225 patent; no esters or amides are mentioned or taught as antiinflammatory agents for local administration to the eyes, nose and ears.
>
> U.S. Patent No. 5,475,034 discloses topically administrable compositions containing certain amide and ester derivatives of 3-benzyolphenylacetic acid, including nepafenac, useful for treating ophthalmic inflammatory disorders and ocular pain. According to the '035 [sic] patent at Col. 15, lines 35-39, "[s]uch disorders include, but are not limited to uveitis scleritis, episcleritis, keratitis, surgically-induced inflammation and endophthalmitis."

(Kapin at p. 1, l. 30 to p. 2, l. 9.)

[2] Examples of ophthalmic compositions that employ tyloxapol are also described in International Publication No. WO 01/15677 at p. 16, lines 20-35 (Example 4); U.S. Publication No. 2002/0103255 at ¶¶ [0077] and [0081] (Examples 2 and 6); U.S. Patent No. 6,395,746 at col. 6, lines 53-66 (Example 2); U.S. Patent No. 5,998,465 at col. 11, lines 25-37 (Example 2) and U.S. Publication No. 2002/0037929 at ¶ [0051] (Example 1).

Kapin also teaches the following administration regimen:

> Compositions intended for topical ophthalmic administration will typically contain a compound of formula (I) in an amount of from about 0.001 to about 4.0% (w/v)...with 1-2 drops once to several times a day.

(Kapin at p. 6, ll. 4-8.)

C. The '431 Patent

Claims 1-22 of the '431 patent are invalid under 35 U.S.C. § 103(a)[3] as obvious over Ogawa et al., U.S. Patent No. 4,910,225 ("Ogawa") combined with Kapin et al., International Publication No. WO 02/13804 ("Kapin").

1. Differences between the Prior Art and the Claimed Subject Matter

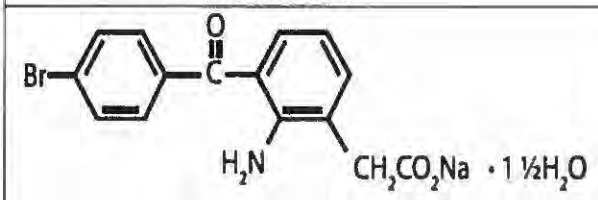
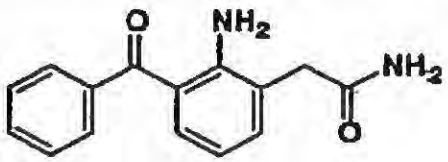
Independent Claim 1 of the '431 patent is directed to an aqueous liquid preparation consisting essentially of the following two components, wherein the first component is 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, wherein the hydrate 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. Independent claim 18 contains the same limitations as claim 1 plus the following required components: boric acid, sodium tetraborate, EDTA sodium salt, benzalkonium chloride, polyvinylpyrrolidone, and sodium sulfite.

Ogawa teaches stable bromfenac sodium ophthalmic compositions which contain benzalkonium chloride, polyvinylpyrrolidone (povidone), sodium sulfite, sodium edetate, boric acid, sodium tetraborate (Borax) and polysorbate 80. While Ogawa does not teach the inclusion of tyloxapol in its compositions, a person of ordinary skill in the art would substitute the polysorbate 80 in Ogawa with the tyloxapol taught by Kapin with a reasonable expectation of success. It is noted that independent claims 1 and 18 recite the transitional phrase "consisting essentially of" and thus cover the recited elements plus only unspecified elements "that do not materially affect the basic and novel characteristics of a composition." *Dow Chem. Co. v. Am. Cyanamid Co.*, 615 F. Supp. 471, 484 (E.D. La. 1985), *aff'd*, 816 F.2d 617 (Fed. Cir. 1987), *cert. denied*, 484 U.S. 849 (1987); *see also PPG Indus. v. Guardian Indus. Corp.*, 156 F.3d 1351, 1354 (Fed. Cir. 1998) ("By using the term 'consisting essentially of,' the drafter signals that the invention necessarily includes the listed ingredients and is open to unlisted ingredients that do not materially affect the basic and novel properties of the invention."). It is further noted that Ogawa also teaches the inclusion of water. Water would not materially affect the

[3] It is noted that the American Invents Act (AIA) has modified 35 U.S.C. §103. The application that became the '431 patent was filed on March 28, 2005 and claimed an "effective filing date" of January 16, 2004 as defined by 35 U.S.C. § 100(i). Because the effective filing date of the '431 patent is before the March 16, 2013 effective date of the AIA amendments, the pre-AIA version of §103 should apply to the analysis of the '431 patent. *See generally* MPEP § 2159.

basic characteristics of the claimed preparation, particularly in view of the preamble of the claim, which indicates that the preparation is an "aqueous liquid."

As discussed above, at the time of filing of the '431 patent, polysorbate 80 and tyloxapol were both well-known non-ionic surfactants that could be used in ophthalmic compositions. A person skilled in the art would have understood that the polysorbate 80 of the Ogawa compositions could be replaced with tyloxapol without affecting stability provided a pH of about 8 was maintained and polyvinylpyrrolidone (povidone) and sodium sulfite were also present in the composition. This understanding is based in part upon the data from Experimental Examples 4-6 of Ogawa. A skilled artisan would further believe that tyloxapol could be substituted for polysorbate 80 without affecting the stability of an aqueous bromfenac composition based on the teachings of Kapin. As discussed above, Kapin exemplifies an aqueous nepafenac ophthalmic composition that employs tyloxapol. Bromfenac and nepafenac are both benzoylphenylacetic acids and have similar structures as shown below:

Bromfenac	Nepafenac
	

Moreover, a person of skill in the art would have been motivated to combine Ogawa and Kapin because Kapin identifies and describes Ogawa in its specification. (Kapin at p. 1, line 30 to p. 2, line 2.)

Dependent claims 2 and 19 limit the 2-amino-3-(4-bromobenzoyl)phenylacetic acid to its sodium salt. The sodium salt of a 2-amino-3-(4-bromobenzoyl)phenylacetic acid is disclosed by Ogawa. (Ogawa at Example 6; Example 8.)

Dependent claims 3-6, 11-12, 15 and 20-22 claim various concentrations, in w/v %, of the bromfenac sodium and tyloxapol components of the liquid preparation. Ogawa discloses concentrations of bromfenac that fall within the claimed ranges. For example:

> "To prepare a liquid preparation, the concentration of the active ingredient [bromfenac] may range from about 0.001% to about 10%, preferably about 0.01% to about 5%."

(Ogawa at col. 4, lines 42-46.) Kapin discloses concentrations of tyloxapol within the claimed ranges. (Kapin at p. 7, lines 13-22.)

Certain of these dependent claims require specific amounts of bromfenac sodium and/or tyloxapol. The determination of the claimed concentration could have been determined by routine optimization. Generally, optimization of ranges will not support the patentability of subject matter encompassed by the prior art. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by

routine experimentation." *In re Aller*, 220 F.2d 454, 456 (CCPA 1955) (claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be *prima facie* obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.).

Dependent claims 7, 8, 13, 14, 16, and 17 claim certain additives included in the liquid preparation. Ogawa teaches all claimed additives. Ogawa discloses:

> According to the present invention, the stability of an aqueous composition . . . 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 include polyvinyl pyrrolidone . . . . The pH adjustment is generally conducted with sodium hydroxide . . . and it is advisable to form a buffer solution by combined use of, for example . . . sodium borate . . . and . . . boric acid . . . .

(Ogawa at col. 3, lines 48-67.) Ogawa also disclosures:

> The preservative includes paraoxybenzoic acid esters, benzyl alcohol, parachloro-meta-xylenol, chlorocresol, phenetyl alcohol, sorbic acid and salts thereof, thimerosal, chlorobutanol, and the like. The chelating agent is, for example, sodium edetate . . . .

(Ogawa at col. 4, lines 29-35.)

Dependent claims 9 and 10 claim pH ranges for the liquid preparation. As indicated above, Ogawa teaches those ranges. (Ogawa at col. 3, ll. 48-67.)

Based on the teachings of Ogawa regarding preparation of stable aqueous bromfenac compositions and that tyloxapol is interchangeable with polysorbate 80 as exemplified by Kapin, a person of skill in the art could easily modify the bromfenac compositions described in Examples 6 and 8 of Ogawa to arrive at the compositions recited in the claims of the '431 patent with more than a reasonable expectation of success.

2. Secondary Considerations

Watson is unaware of any evidence of secondary considerations of non-obviousness of substantive probative value.

D. The '290 Patent

Claims 1-30 of the '290 Patent are invalid under 35 U.S.C. § 103(a)[4] as obvious over Ogawa et al., U.S. Patent No. 4,910,225 ("Ogawa") combined with Kapin et al., International Application Publication No. WO 02/13804.

1. Differences between the Prior Art and the Claimed Subject Matter

Independent Claim 1 of the '290 is directed to an aqueous liquid preparation comprising two components, 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 and the second component is tyloxapol, wherein said liquid preparation is formulated for ophthalmic administration.

Ogawa teaches stable bromfenac sodium ophthalmic compositions which contain benzalkonium chloride, povidone, sodium sulfite, sodium edetate, boric acid, sodium tetraborate and polysorbate 80. While Ogawa does not teach the inclusion of tyloxapol in its compositions, a person of ordinary skill in the art would, as discussed above regarding the '431 patent, substitute the polysorbate 80 in Ogawa with the tyloxapol taught by Kapin with a reasonable expectation of success.

Dependent claim 2 limits the liquid preparation of claim 1 to one further comprising a quaternary ammonium salt. Ogawa teaches stable bromfenac sodium ophthalmic compositions which contain benzalkonium chloride, a quaternary ammonium salt. (Ogawa at Example 6; Example 8.)

Dependent claim 3 limits the 2-amino-3-(4-bromobenzoyl)phenylacetic acid to its sodium salt. The sodium salt of 2-amino-3-(4-bromobenzoyl)phenylacetic acid is disclosed by Ogawa. (Ogawa at Example 6; Example 8.)

Dependent claims 4 and 5 claim various concentrations, in w/v %, of the bromfenac and tyloxapol components of the liquid preparation. Ogawa discloses concentrations of bromfenac that fall within the claimed ranges. For example:

> "To prepare a liquid preparation, the concentration of the active ingredient [bromfenac] may range from about 0.001% to about 10%, preferably about 0.01% to about 5%."

(Ogawa at col. 4, lines 42-46.) Kapin discloses concentrations of tyloxapol within the claimed ranges. (Kapin at p. 7, lines 13-22.)

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[4] It is noted that the American Invents Act (AIA) has modified 35 U.S.C. § 103. The application that became the '290 patent was filed on November 28, 2012 and claimed an "effective filing date" of January 16, 2004 as defined by 35 U.S.C. § 100(i). Because the effective filing date of the '290 patent is before the March 16, 2013 effective date of the AIA amendments, the pre-AIA version of §103 should apply to the analysis of the '290 patent. *See generally* MPEP § 2159.

Dependent claim 6 claims a pH range of the liquid preparation of claim 1. Ogawa discloses bromfenac sodium compositions with pH values that fall within the claimed range. (Ogawa at col. 3, lines 48-67.)

Dependent claim 7 further limits the stable aqueous liquid preparation of claim 1 to one consisting 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 %.

Ogawa teaches stable bromfenac sodium ophthalmic compositions which contain benzalkonium chloride, povidone, sodium sulfite, sodium edetate, boric acid, sodium tetraborate and polysorbate 80. While Ogawa does not teach the inclusion of tyloxapol in its compositions, a person of ordinary skill in the art would substitute the polysorbate 80 in Ogawa with the tyloxapol taught by Kapin with a reasonable expectation of success. Ogawa discloses concentrations of bromfenac that fall within the claimed ranges. (Ogawa at col. 4, lines 42-46.) It is noted that dependent claim 7 recites the transitional phrase "consisting essentially of" and thus cover the recited elements plus only unspecified elements "that do not materially affect the basic and novel characteristics of a composition." *Dow Chem. Co. v. Am. Cyanamid Co.*, 615 F. Supp. 471, 484 (E.D. La. 1985), *aff'd*, 816 F.2d 617 (Fed. Cir. 1987), *cert. denied*, 484 U.S. 849 (1987). It is noted that Ogawa also teaches the inclusion of water. Water would not materially affect the basic characteristics of the claimed preparation, particularly in view of the preamble of the claim, which indicates that the preparation is an "aqueous liquid."

Independent Claim 8 of the '290 patent is directed to an aqueous liquid preparation comprising two components, 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 and the second component is tyloxapol, wherein said liquid preparation is formulated for ophthalmic administration and greater than about 90% of the original amount of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid remains in the preparation after storage at 4 weeks at 60° C.

Ogawa teaches stable bromfenac sodium ophthalmic compositions which contain benzalkonium chloride, povidone, sodium sulfite, sodium edetate, boric acid, sodium tetraborate and polysorbate 80. While Ogawa does not teach the inclusion of tyloxapol in its compositions, a person of ordinary skill in the art would substitute the polysorbate 80 in Ogawa with the tyloxapol taught by Kapin with a reasonable expectation of success.

Ogawa also teaches stable bromfenac sodium ophthalmic compositions that have undergone stability testing for 4 weeks at 60° C. Ogawa reports the results of stability testing showing that greater than about 90% of the original amount of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid remains in the preparation after storage at 4 weeks at 60° C. and states that

> it was found that changes in appearances of the compositions were not observed at all, and the decomposition of the compound was not almost observed, the aqueous compositions being stable, excellent for a long period of time.

(Ogawa, at col.10, ll.50-57; col.14, ll.47-50, 61-63 (Table 11)).

Dependent claim 9 limits the liquid preparation of claim 8 to one further comprising a quaternary ammonium salt. Ogawa teaches stable bromfenac sodium compositions which contain benzalkonium chloride, a quaternary ammonium salt. (Ogawa at Example 6; Example 8.)

Dependent claim 10 limits the preparation of claim 8 to one where greater than 92% of the original amount of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid remains in the preparation after storage at 4 weeks at 60° C. Ogawa discloses this limitation. (Ogawa, at col.10, ll.50-57; col.14, ll.47-50, 61-63 (Table 11)).

Dependent claim 11 claims various concentrations, in w/v %, of the bromfenac and tyloxapol components of the liquid preparation. Ogawa discloses concentrations of bromfenac that fall within the claimed ranges. For example:

> "To prepare a liquid preparation, the concentration of the active ingredient [bromfenac] may range from about 0.001% to about 10%, preferably about 0.01% to about 5%."

(Ogawa at col. 4, lines 42-46.) Kapin discloses concentrations of tyloxapol within the claimed ranges. (Kapin at p. 7, lines 13-22.)

Dependent claim 12 claims a pH range of the liquid preparation of claim 8. Ogawa claims pH values that fall within the claimed range. (Ogawa at col. 3, lines 48-67.)

Dependent claim 13 further limits the stable aqueous liquid preparation of claim 1 to one 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, 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 %.

Ogawa teaches stable bromfenac sodium ophthalmic compositions which contain benzalkonium chloride, povidone, sodium sulfite, sodium edetate, boric acid, sodium tetraborate and polysorbate 80. While Ogawa does not teach the inclusion of tyloxapol in its compositions, a person of ordinary skill in the art would substitute the polysorbate 80 in Ogawa with the tyloxapol taught by Kapin with a reasonable expectation of success. Ogawa discloses concentrations of bromfenac that fall within the claimed ranges. (Ogawa at col. 4, lines 42-46.) It is noted that dependent claim 13 recites the transitional phrase "consisting essentially of" and

thus cover the recited elements plus only unspecified elements "that do not materially affect the basic and novel characteristics of a composition." *Dow Chem. Co. v. Am. Cyanamid Co.*, 615 F. Supp. 471, 484 (E.D. La. 1985), *aff'd*, 816 F.2d 617 (Fed. Cir. 1987), *cert. denied*, 484 U.S. 849 (1987). It is noted that Ogawa also teaches the inclusion of water. Water would not materially affect the basic characteristics of the claimed preparation, particularly in view of the preamble of the claim, which indicates that the preparation is an "aqueous liquid."

Independent Claim 14 of the '290 patent is essentially similar to independent claim 1 with the further limitation that the liquid preparation does not include mannitol. As explained above claim 14 is obvious for the same reasons as provided for independent claim 1. Further, both Ogawa and Kapin disclose ophthalmic preparations that do not include mannitol.

Dependent claim 15 limits the liquid preparation of claim 14 to one further comprising a quaternary ammonium salt. Ogawa teaches stable bromfenac sodium ophthalmic compositions which contain benzalkonium chloride, a quaternary ammonium salt. (Ogawa at Example 6; Example 8.)

Dependent claim 16 limits the 2-amino-3-(4-bromobenzoyl)phenylacetic acid to its sodium salt. The sodium salt of 2-amino-3-(4-bromobenzoyl)phenylacetic acid is disclosed by Ogawa. (Ogawa at Example 6; Example 8.)

Dependent claim 17 claims concentrations, in w/v %, of the bromfenac and tyloxapol components of the liquid preparation. Ogawa discloses concentrations of bromfenac that fall within the claimed range. (Ogawa at col. 4, lines 42-46.) Kapin discloses concentrations of tyloxapol within the claimed range. (Kapin at p. 7, lines 13-22.)

Dependent claim 18 claims a pH range of the liquid preparation of claim 17. Ogawa discloses bromfenac sodium compositions with pH values that fall within the claimed range. (Ogawa at col. 3, lines 48-67.)

Dependent claim 19 further limits the stable aqueous liquid preparation of claim 14 to one 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, 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 %.

Ogawa teaches stable bromfenac sodium ophthalmic compositions which contain benzalkonium chloride, povidone, sodium sulfite, sodium edetate, boric acid, sodium tetraborate and polysorbate 80. While Ogawa does not teach the inclusion of tyloxapol in its compositions, a person of ordinary skill in the art would substitute the polysorbate 80 in Ogawa with the tyloxapol taught by Kapin with a reasonable expectation of success. Ogawa further discloses concentrations of bromfenac that fall within the claimed range. (Ogawa at col. 4, lines 42-46.) It is noted that dependent claim 19 recites the transitional phrase "consisting essentially of" and thus cover the recited elements plus only unspecified elements "that do not materially affect the

basic and novel characteristics of a composition." *Dow Chem. Co. v. Am. Cyanamid Co.*, 615 F. Supp. 471, 484 (E.D. La. 1985), *aff'd*, 816 F.2d 617 (Fed. Cir. 1987), *cert. denied*, 484 U.S. 849 (1987). It is noted that Ogawa also teaches the inclusion of water. Water would not materially affect the basic characteristics of the claimed preparation, particularly in view of the preamble of the claim, which indicates that the preparation is an "aqueous liquid."

Dependent claim 20 further limits the liquid preparation of independent claim 14 to one in which greater than 90% of the original amount of the 2-amino-3-(4-bromobenzoyl) phenylacetic acid remains in the preparation after storage at about 60° C. for 4 weeks. Ogawa discloses liquid preparations containing 2-amino-3-(4-bromobenzoyl) phenylacetic acid that show greater than 90 percent of the 2-amino-3-(4-bromobenzoyl) phenylacetic acid remains after storage for 4 weeks at 60° C. (Ogawa, at col.10, ll.50-57; col.14, ll.47-50, 61-63 (Table 11).)

Dependent claim 21 limits the liquid preparation of claim 20 to one further comprising a quaternary ammonium salt. Ogawa teaches stable bromfenac sodium compositions which contain benzalkonium chloride, a quaternary ammonium salt. (Ogawa at Example 6; Example 8.)

Dependent claim 22 further limits the liquid preparation of independent claim 20 to one in which greater than 92% of the original amount of the 2-amino-3-(4-bromobenzoyl) phenylacetic acid remains in the preparation after storage at about 60° C. for 4 weeks. Ogawa discloses liquid preparations containing 2-amino-3-(4-bromobenzoyl) phenylacetic acid that show greater than 92 percent of the 2-amino-3-(4-bromobenzoyl) phenylacetic acid remains after storage for 4 weeks at 60° C. (Ogawa, at col.10, ll.50-57; col.14, ll.47-50, 61-63 (Table 11).)

Dependent claim 23 claims concentrations, in w/v %, of the bromfenac and tyloxapol components of the liquid preparation of claim 20. Ogawa discloses concentrations of bromfenac that fall within the claimed range. (Ogawa at col. 4, lines 42-46.) Kapin discloses concentrations of tyloxapol within the claimed ranges. (Kapin at p. 7, lines 13-22.)

Dependent claim 24 claims a pH range of the liquid preparation of claim 23. Ogawa discloses bromfenac sodium compositions with pH values that fall within the claimed range. (Ogawa at col. 3, lines 48-67.)

Dependent claim 25 further limits the stable aqueous liquid preparation of claim 20 to one 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, and (h) sodium sulfite, wherein the 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 %.

Ogawa teaches stable bromfenac sodium ophthalmic compositions which contain benzalkonium chloride, povidone, sodium sulfite, sodium edetate, boric acid, sodium tetraborate and polysorbate 80. While Ogawa does not teach the inclusion of tyloxapol in its compositions, a person of ordinary skill in the art would substitute the polysorbate 80 in Ogawa with the tyloxapol taught by Kapin with a reasonable expectation of success. Ogawa discloses concentrations of bromfenac that fall within the claimed ranges. (Ogawa at col. 4, lines 42-46.) It is noted that dependent claim25 recites the transitional phrase "consisting essentially of" and thus cover the recited elements plus only unspecified elements "that do not materially affect the basic and novel characteristics of a composition." *Dow Chem. Co. v. Am. Cyanamid Co.*, 615 F. Supp. 471, 484 (E.D. La. 1985), *aff'd*, 816 F.2d 617 (Fed. Cir. 1987), *cert. denied*, 484 U.S. 849 (1987). It is noted that Ogawa also teaches the inclusion of water. Water would not materially affect the basic characteristics of the claimed preparation, particularly in view of the preamble of the claim, which indicates that the preparation is an "aqueous liquid."

Dependent claims 26-30 further limit the liquid preparations of claims 1, 8, 14, 20 and 22 to one satisfying specific requirements of the preservative efficacy standard of EP-criteria B of the European Pharmacopoeia. The combination of Ogawa and Kapin would lead to a composition which inherently possesses the preservative efficacy claimed in claims 26-30.

Based on the teachings of Ogawa regarding preparation of stable aqueous bromfenac compositions and that tyloxapol is interchangeable with polysorbate 80 as exemplified by Kapin, a person of skill in the art could easily modify the bromfenac compositions described in Examples 6 and 8 of Ogawa to arrive at the compositions recited in the claims of the '290 Patent with more than a reasonable expectation of success.

2. Secondary Considerations

Watson is unaware of any evidence of secondary considerations of non-obviousness of substantive probative value.

E. The '131 Patent

Claims 1-30 of the '131 Patent are invalid under 35 U.S.C. § 103(a)[5] as obvious over Ogawa et al., U.S. Patent No. 4,910,225 ("Ogawa") combined with Kapin et al., International Publication No. WO 02/13804 ("Kapin").

1. Differences between the Prior Art and the Claimed Subject Matter

Independent Claim 1 of the '131 patent is directed to an 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

[5] It is noted that the American Invents Act (AIA) has modified 35 U.S.C. §103. The application that became the '131 patent was filed on January 28, 2014 but claimed an "effective filing date" of January 16, 2004 as defined by 35 U.S.C. § 100(i). Because the effective filing date of the '131 patent is before the March 16, 2013 effective date of the AIA amendments, the pre-AIA version of §103 should apply to the analysis of the '131 patent. *See generally* MPEP § 2159.

hydrate thereof, wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate; the first component is the sole pharmaceutical active ingredient contained in the preparation and is present in the preparation at a concentration from about 0.05 w/v % to about 0.2 w/v %; the second component is tyloxapol and is present in said liquid preparation in an amount sufficient to stabilize said first component; and wherein said stable liquid preparation is formulated for ophthalmic administration.

Ogawa teaches stable bromfenac sodium ophthalmic compositions which contain benzalkonium chloride, povidone, sodium sulfite, sodium edetate, boric acid, sodium tetraborate and polysorbate 80. Ogawa further teaches concentrations of bromfenac sodium within the range claimed in claim 1. (Ogawa at col. 4, lines 42-26.) While Ogawa does not teach the inclusion of tyloxapol in its compositions, a person of ordinary skill in the art would, as discussed, substitute the polysorbate 80 in Ogawa with the tyloxapol taught by Kapin with a reasonable expectation of success.

Dependent claim 2 limits the liquid preparation of claim 1 to one further comprising a quaternary ammonium salt. Ogawa teaches stable bromfenac sodium ophthalmic compositions which contain benzalkonium chloride, a quaternary ammonium salt. (Ogawa at Example 6; Example 8.)

Dependent claim 3 limits the 2-amino-3-(4-bromobenzoyl)phenylacetic acid to its sodium salt. The sodium salt of 2-amino-3-(4-bromobenzoyl)phenylacetic acid is disclosed by Ogawa. (Ogawa at Example 6; Example 8.)

Dependent claim 4 claims a range of concentration, in w/v %, of the tyloxapol components of the liquid preparation. Kapin discloses concentrations of tyloxapol within the claimed range. (Kapin at p. 7, lines 13-22.)

Dependent claim 5 claims a pH range of the liquid preparation of claim 1. Ogawa discloses bromfenac sodium compositions with pH values that fall within the claimed range. (Ogawa at col. 3, lines 48-67.)

Dependent claim 6 further limits the stable aqueous liquid preparation of claim 1 to one consisting 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 % and wherein the concentration of tyloxapol is from about 0.01 w/v % to about 0.05 w/v %.

Ogawa teaches stable bromfenac sodium ophthalmic compositions which contain benzalkonium chloride, povidone, sodium sulfite, sodium edetate, boric acid, sodium tetraborate and polysorbate 80. While Ogawa does not teach the inclusion of tyloxapol in its compositions, a person of ordinary skill in the art would substitute the polysorbate 80 in Ogawa with the tyloxapol taught by Kapin with a reasonable expectation of success. Ogawa further discloses concentrations of bromfenac sodium that fall within the claimed range. For example:

> "To prepare a liquid preparation, the concentration of the active ingredient [bromfenac] may range from about 0.001% to about 10%, preferably about 0.01% to about 5%."

(Ogawa at col. 4, lines 42-46.) Kapin discloses concentrations of tyloxapol within the claimed ranges. (Kapin at p. 7, lines 13-22.) It is noted that dependent claim 6 recites the transitional phrase "consisting essentially of" and thus cover the recited elements plus only unspecified elements "that do not materially affect the basic and novel characteristics of a composition." *Dow Chem. Co. v. Am. Cyanamid Co.*, 615 F. Supp. 471, 484 (E.D. La. 1985), *aff'd*, 816 F.2d 617 (Fed. Cir. 1987), *cert. denied*, 484 U.S. 849 (1987). It is noted that Ogawa also teaches the inclusion of water. Water would not materially affect the basic characteristics of the claimed preparation, particularly in view of the preamble of the claim, which indicates that the preparation is an "aqueous liquid."

Independent claim 7 is similar to claim 1 with the further limitation that the preparation is characterized in that greater than about 90% of the original amount of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt remains in the preparation after storage at about 60° C for 4 weeks. For the reasons discussed above for claim 1, claim 7 is obvious under 35 U.S.C. § 103(a) over Ogawa combined with Kapin. Ogawa also teaches stable bromfenac sodium ophthalmic compositions that have undergone stability testing for 4 weeks at 60° C. Ogawa reports the results of stability testing showing greater than about 90% of the original amount of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt remains in the preparation after storage at about 60° C for 4 weeks and states that:

> it was found that changes in appearances of the compositions were not observed at all, and the decomposition of the compound was not almost observed, the aqueous compositions being stable, excellent for a long period of time.

(Ogawa, at col.10, ll.50-57; col.14, ll.47-50, 61-63 (Table 11).)

Dependent claim 8 limits the liquid preparation of claim 7 to one further comprising a quaternary ammonium salt. Ogawa teaches stable bromfenac sodium ophthalmic compositions which contain benzalkonium chloride, a quaternary ammonium salt. (Ogawa at Example 6; Example 8.)

Dependent claim 9 further limits the composition of claim 7 to one where greater than 92% of the original amount of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid remains in the preparation after storage at 4 weeks at 60° C. Ogawa discloses this limitation. (Ogawa, at col.10, ll.50-57; col.14, ll.47-50, 61-63 (Table 11)).

Dependent claim 10 claims concentrations, in w/v %, of bromfenac sodium and tyloxapol components of the liquid preparation. Ogawa discloses the claimed concentration of bromfenac sodium. (Ogawa at col. 4, ll. 42-46.) Kapin discloses concentrations of tyloxapol within the claimed range. (Kapin at p. 7, lines 13-22.).

Dependent claim 11 claims a pH range of the liquid preparation of claim 10. Ogawa discloses pH values that fall within the claimed range. (Ogawa at col. 3, lines 48-67.)

Dependent claim 12 further limits the preparation of claim 7 to one where the stable aqueous liquid preparation consists essentially of: (a) 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate; (b) tyloxapol; (c) boric acid; (d) sodium tetraborate; (e) EDTA sodium salt; (f) benzalkonium chloride; (g) polyvinylpyrrolidone; and (h) sodium sulfite; and wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.05 w/v % to about 0.1 w/v %, and the concentration of tyloxapol is about 0.02 w/v %.

Ogawa teaches stable bromfenac sodium ophthalmic compositions which contain benzalkonium chloride, povidone, sodium sulfite, sodium edetate, boric acid, sodium tetraborate and polysorbate 80. While Ogawa does not teach the inclusion of tyloxapol in its compositions, a person of ordinary skill in the art would substitute the polysorbate 80 in Ogawa with the tyloxapol taught by Kapin with a reasonable expectation of success. Ogawa discloses concentrations of bromfenac sodium that fall within the claimed range. (Ogawa at col. 4, lines 42-46.) Kapin discloses concentrations of tyloxapol within the claimed ranges. (Kapin at p. 7, lines 13-22.) It is noted that dependent claim 12 recites the transitional phrase "consisting essentially of" and thus cover the recited elements plus only unspecified elements "that do not materially affect the basic and novel characteristics of a composition." *Dow Chem. Co. v. Am. Cyanamid Co.*, 615 F. Supp. 471, 484 (E.D. La. 1985), *aff'd*, 816 F.2d 617 (Fed. Cir. 1987), *cert. denied*, 484 U.S. 849 (1987). It is noted that Ogawa also teaches the inclusion of water. Water would not materially affect the basic characteristics of the claimed preparation, particularly in view of the preamble of the claim, which indicates that the preparation is an "aqueous liquid."

Independent claim 13 claims the same limitations as independent claim 1 with the further limitation that the preparation does not contain mannitol. For the reasons discussed above for claim 1, claim 13 is obvious under 35 U.S.C. § 103(a) over Ogawa combined with Kapin. Ogawa further teaches bromfenac sodium ophthalmic compositions that do not contain mannitol. (Ogawa at Example 6; Example 8.)

Dependent claim 14 limits the liquid preparation of claim 13 to one further comprising a quaternary ammonium salt. Ogawa teaches stable bromfenac sodium ophthalmic compositions which contain benzalkonium chloride, a quaternary ammonium salt. (Ogawa at Example 6; Example 8.)

Dependent claim 15 limits the 2-amino-3-(4-bromobenzoyl)phenylacetic acid of claim 13 to its sodium salt. The sodium salt of 2-amino-3-(4-bromobenzoyl)phenylacetic acid is disclosed by Ogawa. (Ogawa at Example 6; Example 8.)

Dependent claim 16 claims a range of concentration, in w/v %, of the tyloxapol and the 2-amino-3-(4-bromobenzoyl)phenylacetic acid components of the liquid preparation. Ogawa

discloses concentrations of bromfenac sodium that fall within the claimed range. (Ogawa at col. 4, lines 42-46.) Kapin discloses concentrations of tyloxapol within the claimed range. (Kapin at p. 7, lines 13-22.)

Dependent claim 17 claims a pH range of the liquid preparation of claim 13. Ogawa discloses pH values that fall within the claimed range. (Ogawa at col. 3, lines 48-67.)

Dependent claim 18 further limits the preparation of claim 13 wherein the stable aqueous liquid preparation consists essentially of: (a) 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate; (b) tyloxapol; (c) boric acid; (d) sodium tetraborate; (e) EDTA sodium salt; (f) benzalkonium chloride; (g) polyvinylpyrrolidone; and (h) sodium sulfite; 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 %, and the concentration of tyloxapol is about 0.02 w/v % to about 0.05 w/v %.

Ogawa teaches stable bromfenac sodium ophthalmic compositions which contain benzalkonium chloride, povidone, sodium sulfite, sodium edetate, boric acid, sodium tetraborate and polysorbate 80. While Ogawa does not teach the inclusion of tyloxapol in its compositions, a person of ordinary skill in the art would substitute the polysorbate 80 in Ogawa with the tyloxapol taught by Kapin with a reasonable expectation of success. Ogawa further discloses concentrations of bromfenac sodium that fall within the claimed range. (Ogawa at col. 4, lines 42-46.) Kapin discloses concentrations of tyloxapol within the claimed ranges. (Kapin at p. 7, lines 13-22.) It is noted that dependent claim 18 recites the transitional phrase "consisting essentially of" and thus cover the recited elements plus only unspecified elements "that do not materially affect the basic and novel characteristics of a composition." *Dow Chem. Co. v. Am. Cyanamid Co.*, 615 F. Supp. 471, 484 (E.D. La. 1985), *aff'd*, 816 F.2d 617 (Fed. Cir. 1987), *cert. denied*, 484 U.S. 849 (1987). It is noted that Ogawa also teaches the inclusion of water. Water would not materially affect the basic characteristics of the claimed preparation, particularly in view of the preamble of the claim, which indicates that the preparation is an "aqueous liquid."

Dependent claim 19 limits the preparation of claim 13 to one where greater than about 90% of the original amount of the first component remains in the preparation after storage at about 60° C for 4 weeks. Ogawa teaches this limitation. (Ogawa, at col.10, ll.50-57; col.14, ll.47-50, 61-63 (Table 11).)

Dependent claim 20 limits the liquid preparation of claim 19 to one further comprising a quaternary ammonium salt. Ogawa teaches stable bromfenac sodium ophthalmic compositions which contain benzalkonium chloride, a quaternary ammonium salt. (Ogawa at Example 6; Example 8.)

Dependent claim 21 limits the preparation of claim 19 to one where 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. Ogawa teaches this limitation. (Ogawa, at col.10, ll.50-57; col.14, ll.47-50, 61-63 (Table 11).)

Dependent claim 22 further limits the preparation of claim 21 to certain concentrations of tyloxapol and bromfenac sodium. Ogawa discloses concentrations of bromfenac sodium that fall within the claimed range. (Ogawa at col. 4, lines 42-46.) Kapin discloses concentrations of tyloxapol within the claimed range. (Kapin at p. 7, lines 13-22.)

Dependent claim 23 claims a pH range of the liquid preparation of claim 22. Ogawa discloses pH values that fall within the claimed range. (Ogawa at col. 3, lines 48-67.)

Dependent claim 24 further limits the preparation of claim 13 wherein the stable aqueous liquid preparation consists essentially of: (a) 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate; (b) tyloxapol; (c) boric acid; (d) sodium tetraborate; (e) EDTA sodium salt; (f) benzalkonium chloride; (g) polyvinylpyrrolidone; and (h) sodium sulfite; and wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.05 w/v % to about 0.1 w/v %.

Ogawa teaches stable bromfenac sodium ophthalmic compositions which contain benzalkonium chloride, povidone, sodium sulfite, sodium edetate, boric acid, sodium tetraborate and polysorbate 80. While Ogawa does not teach the inclusion of tyloxapol in its compositions, a person of ordinary skill in the art would substitute the polysorbate 80 in Ogawa with the tyloxapol taught by Kapin with a reasonable expectation of success. Ogawa also discloses concentrations of bromfenac sodium that fall within the claimed range. (Ogawa at col. 4, lines 42-46.) It is noted that dependent claim 24 recites the transitional phrase "consisting essentially of" and thus cover the recited elements plus only unspecified elements "that do not materially affect the basic and novel characteristics of a composition." *Dow Chem. Co. v. Am. Cyanamid Co.*, 615 F. Supp. 471, 484 (E.D. La. 1985), *aff'd*, 816 F.2d 617 (Fed. Cir. 1987), *cert. denied*, 484 U.S. 849 (1987). It is noted that Ogawa also teaches the inclusion of water. Water would not materially affect the basic characteristics of the claimed preparation, particularly in view of the preamble of the claim, which indicates that the preparation is an "aqueous liquid."

Dependent claims 25-29 further limit the liquid preparations of claims 1, 4, 7, 9 and 13 to one satisfying specific requirements of the preservative efficacy standard of US Pharmacopoeia. The combination of Ogawa and Kapin would lead to a composition which inherently possesses the preservative efficacy recited in claims 25-29.

Dependent claim 30 limits the composition of claim 1 to one further comprising one or more additives selected from the group consisting of a preservative, buffer, thickener, stabilizer, chelating agent, and pH controlling agent. Ogawa teaches compositions containing one or more of these additives. Ogawa discloses:

> According to the present invention, the stability of an aqueous composition . . . 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 include polyvinyl pyrrolidone . . . . The pH adjustment is generally

> conducted with sodium hydroxide . . . and it is advisable to form a buffer solution by combined use of, for example . . . sodium borate . . . and . . . boric acid . . . .

(Ogawa at col. 3, lines 48-67.) Ogawa also disclosures:

> The preservative includes paraoxybenzoic acid esters, benzyl alcohol, parachloro-meta-xylenol, chlorocresol, phenetyl alcohol, sorbic acid and salts thereof, thimerosal, chlorobutanol, and the like. The chelating agent is, for example, sodium edetate . . . .

(Ogawa at col. 4, lines 29-35.)

Based on the teachings of Ogawa regarding preparation of stable aqueous bromfenac compositions and that tyloxapol is interchangeable with polysorbate 80 as exemplified by Kapin, a person of skill in the art could easily modify the bromfenac compositions described in Examples 6 and 8 of Ogawa to arrive at the compositions recited in the claims of the '131 Patent with more than a reasonable expectation of success.

2. Secondary Considerations

Watson is unaware of any evidence of secondary considerations of non-obviousness of substantive probative value.

F. The '813 Patent

Claims 1-5, 7-11, 13-17, 19-22 and 27 of the '813 Patent are invalid under 35 U.S.C. § 103(a)[6] as obvious over Ogawa et al., U.S. Patent No. 4,910,225 ("Ogawa") combined with Kapin et al., International Publication No. WO 02/13804 ("Kapin").

1. Differences between the Prior Art and the Claimed Subject Matter

Independent Claim 1 of the '813 patent is directed to an aqueous liquid preparation consisting essentially of: a) a first component; and (b) a second component; wherein the first component is 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof; (c) boric acid; (d) sodium tetraborate; and (e) water; wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate; the first component is the sole pharmaceutical active ingredient contained in the preparation and is present in the preparation at a concentration from about 0.05 w/v % to about 0.2 w/v %; the second component is tyloxapol and is present in said liquid preparation in an amount sufficient

[6] It is noted that the American Invents Act (AIA) has modified 35 U.S.C. §103. The application that became the '813 patent was filed on April 25, 2014 but claimed an "effective filing date" of January 16, 2004 as defined by 35 U.S.C. § 100(i). Because the effective filing date of the '813 patent is before the March 16, 2013 effective date of the AIA amendments, the pre-AIA version of §103 should apply to the analysis of the '813 patent. *See generally* MPEP § 2159.

to stabilize said first component; and wherein said stable liquid preparation is formulated for ophthalmic administration.

Ogawa teaches stable bromfenac sodium ophthalmic monohydrate compositions which contain bromfenac sodium monohydrate within the claimed concentration and further contains boric acid, sodium tetraborate, polysorbate 80 and water. While Ogawa does not teach the inclusion of tyloxapol in its compositions, a person of ordinary skill in the art would, as discussed above, substitute the polysorbate 80 in Ogawa with the tyloxapol taught by Kapin with a reasonable expectation of success.

It is noted that independent claim 1 of the '813 patent recites the transitional phrase "consisting essentially of" and thus cover the recited elements plus only unspecified elements "that do not materially affect the basic and novel characteristics of a composition." *Dow Chem. Co. v. Am. Cyanamid Co.*, 615 F. Supp. 471, 484 (E.D. La. 1985), *aff'd*, 816 F.2d 617 (Fed. Cir. 1987), *cert. denied*, 484 U.S. 849 (1987); *see also PPG Indus. v. Guardian Indus. Corp.*, 156 F.3d 1351, 1354 (Fed. Cir. 1998) ("By using the term 'consisting essentially of,' the drafter signals that the invention necessarily includes the listed ingredients and is open to unlisted ingredients that do not materially affect the basic and novel properties of the invention."). In addition to the ingredients recited in claim 1 of the '813 patent, Example 6 of Ogawa includes disodium edetate, benzalkonium chloride, polyvinyl pyrrolidone (*i.e.*, povidone) and sodium sulfite, and Example 8 of Ogawa includes benzalkonium chloride, polyvinyl pyrrolidone (*i.e.*, povidone) and sodium sulfite. The presence of disodium edetate, benzalkonium chloride, povidone and sodium sulfite, as taught by Ogawa, would not materially affect the basic and novel characteristics of the compositions recited in the '813 patent because these ingredients contribute to the stability of an aqueous bromfenac composition and do not impart different qualities on such a composition. Dependent claims 2, 6, 8, 12, 14, 18, 23 and 27 which recite the addition of disodium edetate, povidone and/or sodium sulfite to the preparations of independent claim 1 provide additional support that the presence of disodium edetate, benzalkonium chloride, povidone and sodium sulfite, as taught by Ogawa, would not materially affect the basic and novel characteristics of the compositions recited in the '813 patent. Further support can be found in dependent claims 24-26 which indicate that a preservative, such as benzalkonium chloride, is not required for the preparations of claims 1 and thereby indicates that the preparations of claim 1 may include a preservative.

Dependent claim 2 limits the liquid preparation of claim 1 to one further consisting of sodium sulfite. Ogawa teaches stable bromfenac sodium ophthalmic compositions which contain sodium sulfite. (Ogawa at Example 6; Example 8.)

Dependent claim 3 limits the 2-amino-3-(4-bromobenzoyl)phenylacetic acid to its sodium salt. The sodium salt of 2-amino-3-(4-bromobenzoyl)phenylacetic acid is disclosed by Ogawa. (Ogawa at Example 6; Example 8.)

Dependent claim 4 claims a range of concentration, in w/v %, of the tyloxapol components of the liquid preparation. Kapin discloses concentrations of tyloxapol within the claimed range. (Kapin at p. 7, lines 13-22.)

Dependent claim 5 claims a pH range of the liquid preparation of claim 1. Ogawa discloses bromfenac sodium compositions with pH values that fall within the claimed range. (Ogawa at col. 3, lines 48-67.)

Independent claim 7 is similar to claim 1 with the further limitation that the preparation is characterized in that greater than about 90% of the original amount of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt remains in the preparation after storage at about 60° C for 4 weeks. For the reasons discussed above for claim 1, claim 7 is obvious under 35 U.S.C. § 103(a) over Ogawa combined with Kapin. Ogawa also teaches stable bromfenac sodium ophthalmic compositions that have undergone stability testing for 4 weeks at 60° C. Ogawa reports the results of stability testing showing that greater than about 90% of the original amount of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt remains in the preparation after storage at about 60° C for 4 weeks and states that:

> it was found that changes in appearances of the compositions were not observed at all, and the decomposition of the compound was not almost observed, the aqueous compositions being stable, excellent for a long period of time.

(Ogawa, at col.10, ll.50-57; col.14 ll.47-50, 61-63 (Table 11).)

Dependent claim 8 limits the liquid preparation of claim 7 to one further consisting of sodium sulfite. Ogawa teaches stable bromfenac sodium ophthalmic compositions which contain sodium sulfite. (Ogawa at Example 6; Example 8.)

Dependent claim 9 further limits the composition of claim 7 to one where greater than 92% of the original amount of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid remains in the preparation after storage at 4 weeks at 60° C. Ogawa discloses this limitation. (Ogawa, at col.10, ll.50-57; col.14 ll.47-50, 61-63 (Table 11)).

Dependent claim 10 claims various concentrations, in w/v %, of the bromfenac sodium and tyloxapol components of the liquid preparation of claim 7. Ogawa discloses the claimed concentration of bromfenac sodium. (Ogawa at col. 4, lines 42-46.) Kapin discloses concentrations of tyloxapol within the claimed ranges. (Kapin at p. 7, lines 13-22.). Moreover, as discussed above, the determination of the claimed concentration could have been determined by routine optimization.

Dependent claim 11 claims a pH range of the liquid preparation of claim 10. Ogawa discloses pH values that fall within the claimed range. (Ogawa at col. 3, lines 48-67.)

Independent claim 13 is similar to claim 1 with the further limitation that the preparation does not include mannitol. For the reasons discussed above for claim 1, claim 13 is obvious under 35 U.S.C. § 103(a) over Ogawa combined with Kapin. Ogawa in combination with Kapin disclose stable bromfenac sodium hydroxide ophthalmic compositions without mannitol. (Ogawa at Example 6; Example 8.)

Dependent claim 14 limits the liquid preparation of claim 13 to one further consisting of sodium sulfite. Ogawa teaches stable bromfenac sodium ophthalmic compositions which contain sodium sulfite. (Ogawa at Example 6; Example 8.)

Dependent claim 15 limits the 2-amino-3-(4-bromobenzoyl)phenylacetic acid to its sodium salt. The sodium salt of 2-amino-3-(4-bromobenzoyl)phenylacetic acid is disclosed by Ogawa. (Ogawa at Example 6; Example 8.)

Dependent claim 16 claims various concentrations, in w/v %, of bromfenac sodium and tyloxapol components of the liquid preparation of claim13. Ogawa discloses the claimed concentration of bromfenac sodium. (Ogawa at col. 4, ll. 42-26.) Kapin discloses concentrations of tyloxapol within the claimed range. (Kapin at p. 7, lines 13-22.)

Dependent claim 17 claims a pH range of the liquid preparation of claim 13. Ogawa discloses pH values that fall within the claimed range. (Ogawa at col. 3, lines 48-67.)

Dependent claim 19 further limits the composition of claim 13 to one where greater than 90% of the original amount of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid remains in the preparation after storage at 4 weeks at 60° C. Ogawa teaches stable bromfenac sodium ophthalmic compositions that have undergone stability testing for 4 weeks at 60° C. Ogawa reports the results of stability testing showing that greater than 90% of the original amount of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid remains in the preparation after storage at 4 weeks at 60° C. and states that:

> it was found that changes in appearances of the compositions were not observed at all, and the decomposition of the compound was not almost observed, the aqueous compositions being stable, excellent for a long period of time.

(Ogawa, at col.10, ll.50-57; col.14, ll.47-50, 61-63 (Table 11).)

Dependent claim 20 further limits the composition of claim 13 to one where greater than 92% of the original amount of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid remains in the preparation after storage at 4 weeks at 60° C. Ogawa discloses this limitation. (Ogawa, at col.10, ll.50-57; col.14, ll.47-50, 61-63 (Table 11)).

Dependent claim 21 claims various concentrations, in w/v %, of the bromfenac sodium and tyloxapol components of the liquid preparation of claim 20. Ogawa discloses the claimed concentration of bromfenac sodium. (Ogawa at col. 4, ll. 42-46.) Kapin discloses concentrations of tyloxapol within the claimed range. (Kapin at p. 7, lines 13-22.)

Dependent claim 22 claims a pH range of the liquid preparation of claim 21. Ogawa discloses pH values that fall within the claimed range. (Ogawa at col. 3, lines 48-67.)

Dependent claim 27 further limits claim 1 to one optionally further consisting of one or more additives selected from the group consisting of buffers, thickeners, stabilizers, chelating

agents, and pH controlling agents. Ogawa teaches compositions containing one or more of these additives. Ogawa discloses:

> According to the present invention, the stability of an aqueous composition . . . 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 include polyvinyl pyrrolidone . . . . The pH adjustment is generally conducted with sodium hydroxide . . . and it is advisable to form a buffer solution by combined use of, for example . . . sodium borate . . . and . . . boric acid . . . .

(Ogawa at col. 3, lines 48-67.)

2. SECONDARY CONSIDERATIONS

Watson is unaware of any evidence of secondary considerations of non-obviousness of substantive probative value.

G. The '606 Patent

Claims 1-30 of the '606 patent are invalid under 35 U.S.C. § 103(a)[7] as obvious over Ogawa et al., U.S. Patent No. 4,910,225 ("Ogawa") combined with Kapin et al., International Application Publication No. WO 02/13804 ("Kapin").

1. Differences between the Prior Art and the Claimed Subject Matter.

Independent claim 1 of the '606 patent is directed to a method for treating an inflammatory disease of an eye, the method comprising administering to said eye a stable aqueous liquid preparation that comprises: (a) a first component; and (b) a second component; wherein the first component is 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate; the first component is the sole pharmaceutical active ingredient contained in the preparation; the second component is tyloxapol and is present in said liquid preparation in an amount sufficient to stabilize said first component; wherein said stable liquid preparation is formulated for ophthalmic administration; and wherein said liquid preparation is administered to said eye at a dose and a frequency effective to treat said inflammatory disease.

Ogawa teaches a method of treating inflammatory eye disease with stable bromfenac sodium ophthalmic compositions which contain benzalkonium chloride, povidone, sodium

[7] It is noted that the American Invents Act (AIA) has modified 35 U.S.C. §103. The application that became the '606 patent was filed on September 23, 2014 but claimed an "effective filing date" of January 16, 2004 as defined by 35 U.S.C. § 100(i). Because the effective filing date of the '606 patent is before the March 16, 2013 effective date of the AIA amendments, the pre-AIA version of §103 should apply to the analysis of the '606 patent. *See generally* MPEP § 2159.

sulfite, sodium edetate, boric acid, sodium tetraborate and polysorbate 80. Kapin teaches stable ophthalmic compositions comprising 3-benzoylphenlacetic acids and tyloxapol to treat or prevent angiogenic diseases. While Ogawa does not teach the inclusion of tyloxapol in its compositions, a person of ordinary skill in the art would, as discussed above, substitute the polysorbate 80 in Ogawa with the tyloxapol taught by Kapin with a reasonable expectation of success. Further, both Ogawa and Kapin teach that the ophthalmic compositions may be administered topically to a patient's eye with one to several drops administered 1 to 4 times a day.

Dependent claim 2 limits the method of claim 1 to an inflammatory disease of an anterior or posterior segment of an eye. Both Ogawa and Kapin disclose this limitation. (Ogawa at col. 4, ll. 40-59; Kapin at p. 2, ll. 4-9.)

Dependent claim 3 limits the method of claim 2 to where the disease is postoperative inflammation. Kapin discloses this limitation. Specifically Kapin discloses the use of topically administrable compositions containing 3-benzyolphenylacetic acid for treating ophthalmic inflammatory disorders and ocular pain, such as uveitis scleritis, episcleritis, keratitis, surgically-induced inflammation and endophthalmitis. (Kapin at p. 2, ll. 4-9.)

Dependent claim 4 is directed to the method according to claim 1, wherein the first component is a 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt. Ogawa discloses this limitation. (Ogawa at col. 10, ll. 5-18.)

Dependent claims 5, 6 and 8 limit the method of claim 1 to compositions containing specific concentrations of tyloxapol and the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt. Ogawa discloses concentrations of 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt within the claimed range. (Ogawa at col. 4, ll. 42-46.) Kapin discloses a concentration of tyloxapol within the claimed range. (Kapin at p. 7, ll. 13-22.)

Dependent claim 7 limits the method of claim 5 to one where the aqueous liquid preparation further comprises a quaternary ammonium salt. Ogawa discloses compositions containing benzalkonium chloride, which, as noted in the '606 patent at col. 2, ll. 22-24, is a quaternary ammonium salt. (Ogawa at Example 6; Example 8.)

Dependent claim 9 limits the method of claim 1 to one where the stable aqueous 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 %.

As discussed above with regards to claims 1, Ogawa teaches a method of treating inflammatory eye disease with stable bromfenac sodium ophthalmic compositions which contain benzalkonium chloride, povidone, sodium sulfite, sodium edetate, sodium tetraborate and polysorbate 80. Kapin teaches stable ophthalmic compositions comprising 3-benzoylphenlacetic acids and tyloxapol to treat or prevent angiogenic diseases. While Ogawa

does not teach the inclusion of tyloxapol in its compositions, a person of ordinary skill in the art would substitute the polysorbate 80 in Ogawa with the tyloxapol taught by Kapin with a reasonable expectation of success. Further, Ogawa teaches ophthalmic formulations where 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 %. (Ogawa at col. 4, ll. 42-46.)

It is noted that claim 9 uses the transitional phrase "consists essentially of" The transitional phrase "consists essentially of' has typically been interpreted by the courts to mean the claim is limited to the recited ingredients and any additional ingredient that does not materially affect the basic and novel characteristics of the claimed invention. *Dow Chem. Co. v. Am. Cyanamid Co.*, 615 F. Supp. 471, 484 (E.D. La. 1985), *aff'd*, 816 F.2d 617 (Fed. Cir. 1987), *cert. denied*, 484 U.S. 849 (1987); *See also PPG Indus. v. Guardian Indus. Corp.*, 156 F.3d 1351, 1354 (Fed. Cir. 1998) ("By using the term 'consisting essentially of,' the drafter signals that the invention necessarily includes the listed ingredients and is open to unlisted ingredients that do not materially affect the basic and novel properties of the invention.") The formulations taught by Ogawa also teach the inclusion of boric acid and water. Neither boric acid nor water would materially affect the basic characteristics of the claimed preparation, particularly in view of the claim, which requires a "stable aqueous liquid preparation."

Dependent claim 10 limits the method of claim 1 to one where the dose comprises one or two drops. Ogawa teaches:

> [t]he ophthalmic composition of this invention may be administered in accordance with the following schedules. In the form of eye-drops, one to several drops per dose are instilled with a frequency of once to 4 times a day according to the clinical condition.

(Ogawa at col.4, ll. 48-53.) Kapin also discloses this limitation:

> [c]ompositions intended for topical ophthalmic administration will typically contain a compound of formula (I) in an amount of from about 0.001 to about 4.0% (w/v), preferably from about 0.01 to about 0.5% (w/v), with 1-2 drops once to several times a day.

(Kapin at p. 6, ll. 4-8.)

Claim 11 is similar to claim 1 and is directed to a method for treating an inflammatory disease of an eye, the method comprising administering to said eye a stable aqueous liquid preparation that comprises: (a) a first component; and (b) a second component; wherein the first component is 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate; the first component is the sole pharmaceutical active ingredient contained in the preparation; the second component is tyloxapol; wherein said stable liquid preparation is formulated for ophthalmic administration; wherein the stable aqueous liquid preparation is characterized in that greater than about 90% of the original amount of the first

component remains in the preparation after storage at about 60° C. for 4 weeks; and wherein said liquid preparation is administered to said eye at a dose and a frequency effective to treat said inflammatory disease.

As discussed above, Ogawa teaches a method of treating inflammatory eye disease with stable bromfenac sodium ophthalmic compositions which contain benzalkonium chloride, povidone, sodium sulfite, sodium edetate, boric acid, sodium tetraborate and polysorbate 80. Kapin teaches stable ophthalmic compositions comprising 3-benzoylphenlacetic acids and tyloxapol to treat or prevent angiogenic diseases. While Ogawa does not teach the inclusion of tyloxapol in its compositions, a person of ordinary skill in the art would substitute the polysorbate 80 in Ogawa with the tyloxapol taught by Kapin with a reasonable expectation of success.

Claim 11 differs from claim 1 by adding limitations directed to stability as defined by the amount of bromfenac remaining in the preparation after storage at certain conditions for a given amount of time. Ogawa teaches stable bromfenac sodium ophthalmic compositions that have undergone stability testing for 4 weeks at 60° C. Ogawa reports the results of the stability testing and states that:

> [a]s shown in Table 11, it was found that changes in appearances of the compositions were not observed at all, and the decomposition of the compound was not almost observed, the aqueous compositions being stable, excellent for a long period of time."

	Appearance	Residue (%)
Example 6	–	100.9
Example 7	–	99.2
Example 8	–	98.9

(Ogawa, at col.10, ll.50-57; col.1, ll.47-50, 61-63 (Table 11).)

Dependent claim 12 further limits claim 11 to greater than 92% of the original amount of bromfenac remaining in the preparation. As shown above, Ogawa discloses this limitation.

Dependent claim 13 limits the method of claim 11 to an inflammatory disease of an anterior or posterior segment of an eye. Both Ogawa and Kapin disclose this limitation. (Ogawa at col. 4, ll. 49-50; Kapin at p. 2, ll. 4-9.)

Dependent claim 14 limits the method of claim 13 to where the disease is postoperative inflammation. Kapin discloses this limitation. Specifically Kapin discloses the use of topically administrable compositions containing 3-benzyolphenylacetic acid for treating ophthalmic inflammatory disorders and ocular pain, such as uveitis scleritis, episcleritis, keratitis, surgically-induced inflammation and endophthalmitis. (Kapin at p. 2, ll. 4-9.)

Dependent claims 15 and 16 limit the method of claim 11 and 15 respectively to compositions containing specific concentrations of tyloxapol and the 2-amino-3-(4-

bromobenzoyl)phenylacetic acid sodium salt. Ogawa discloses concentrations of 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt within the claimed range. (Ogawa at col. 4, ll. 42-46.) Kapin discloses a concentration of tyloxapol within the claimed range. (Kapin at p. 7, ll. 13-22.)

Dependent claim 17 limits the method of claim 11 to one where the aqueous liquid preparation further comprises a quaternary ammonium salt. Ogawa discloses an composition containing benzalkonium chloride, which as noted in the '606 patent at col. 2, ll. 22-24, is a quaternary ammonium salt. (Ogawa at col. 10, ll. 5-18; Kapin at p. 7, ll. 13-22.)

Dependent claim 18 limits the method of claim 11 to one where 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 %.

Ogawa teaches a method of treating inflammatory eye disease with stable bromfenac sodium ophthalmic compositions which contain benzalkonium chloride, povidone, sodium sulfite, sodium edetate, boric acid, sodium tetraborate and polysorbate 80. Kapin teaches stable ophthalmic compositions comprising 3-benzoylphenlacetic acids and tyloxapol to treat or prevent angiogenic diseases. While Ogawa does not teach the inclusion of tyloxapol in its compositions, a person of ordinary skill in the art would substitute the polysorbate 80 in Ogawa with the tyloxapol taught by Kapin with a reasonable expectation of success. Further, Ogawa teaches ophthalmic formulations where 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 %. (Ogawa at col. 4, ll. 42-46.) It is noted that dependent claim 18 recites the transitional phrase "consisting essentially of" and thus cover the recited elements plus only unspecified elements "that do not materially affect the basic and novel characteristics of a composition." *Dow Chem. Co. v. Am. Cyanamid Co.*, 615 F. Supp. 471, 484 (E.D. La. 1985), *aff'd*, 816 F.2d 617 (Fed. Cir. 1987), *cert. denied*, 484 U.S. 849 (1987). It is noted that the formulations taught by Ogawa also teaches the inclusion of water. Water would not materially affect the basic characteristics of the claimed preparation, particularly in view of the claim, which requires an "aqueous liquid preparation."

Independent claim 19 of the '606 patent is essentially similar to independent claim 1 with the further limitation that the liquid preparation does not include mannitol. As explained above, claim 19 is obvious for the same reasons as provided for independent claim 1. Further, both Ogawa and Kapin disclose ophthalmic preparations that do not include mannitol. (Ogawa at col. 10, ll. 5-18; Ogawa, at col. 10, ll. 35-49; Kapin, at 7, ll. 13-22.)

Dependent claim 20 limits the method of claim 19 to an inflammatory disease of an anterior or posterior segment of an eye. Both Ogawa and Kapin disclose this limitation. (Ogawa at col. 4, ll. 49-50; Kapin at p. 2, ll. 4-9.)

Dependent claim 21 limits the method of claim 20 to where the disease is postoperative inflammation. Kapin discloses this limitation. (Kapin at p. 2, ll. 4-9.)

Dependent claim 22 is directed to the method according to claim 19, wherein the first component is a 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt. Ogawa discloses this limitation. (Ogawa at Example 6; Example 8.)

Dependent claims 23 and 24 limit the method of claim 12 to compositions containing specific concentrations of tyloxapol and the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt. Ogawa discloses concentrations of 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt within the claimed range. (Ogawa at col. 4, ll. 42-46.) Kapin discloses a concentration of tyloxapol within the claimed range. (Kapin at p. 7, ll. 13-22.)

Dependent claim 25 limits the method of claim 20 to one where 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 %.

Ogawa teaches a method of treating inflammatory eye disease with stable bromfenac sodium ophthalmic compositions which contain benzalkonium chloride, povidone, sodium sulfite, sodium edetate, boric acid, sodium tetraborate and polysorbate 80. Kapin teaches stable ophthalmic compositions comprising 3-benzoylphenlacetic acids and tyloxapol to treat or prevent angiogenic diseases. While Ogawa does not teach the inclusion of tyloxapol in its compositions, a person of ordinary skill in the art would substitute the polysorbate 80 in Ogawa with the tyloxapol taught by Kapin with a reasonable expectation of success. Further, Ogawa teaches ophthalmic formulations where 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 %. (Ogawa at col. 4, ll. 42-46.) It is noted that dependent claim 25 recites the transitional phrase "consisting essentially of" and thus cover the recited elements plus only unspecified elements "that do not materially affect the basic and novel characteristics of a composition." *Dow Chem. Co. v. Am. Cyanamid Co.*, 615 F. Supp. 471, 484 (E.D. La. 1985), *aff'd*, 816 F.2d 617 (Fed. Cir. 1987), *cert. denied*, 484 U.S. 849 (1987). It is noted that the formulations taught by Ogawa also teaches the inclusion of water. Water would not materially affect the basic characteristics of the claimed preparation, particularly in view of the claim, which requires an "aqueous liquid preparation."

Dependent claim 26 limits the method of claim 20 to one where the stable aqueous liquid preparation is defined by the amount of bromfenac remaining in the preparation after storage at certain conditions for a given amount of time. Ogawa teaches stable bromfenac sodium ophthalmic compositions that have undergone stability testing for 4 weeks at 60° C. Ogawa reports the results of the stability testing and states that:

[a]s shown in Table 11, it was found that changes in appearances of the compositions were not observed at all, and the decomposition of the compound was not almost observed, the aqueous compositions being stable, excellent for a long period of time."

	Appearance	Residue (%)
Example 6	–	100.9
Example 7	–	99.2
Example 8	–	98.9

(Ogawa, at col.10, ll.50-57; col.14 ll.47-50, 61-63 (Table 11).)

Dependent claim 27 limits the method of claim 20 to compositions containing specific concentrations of tyloxapol and the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt. Ogawa discloses concentrations of 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt within the claimed range. (Ogawa at col. 4, ll. 42-46.) Kapin discloses a concentration of tyloxapol within the claimed range. (Kapin at p. 7, ll. 13-22.)

Dependent claims 28-30 further limit the methods of claims 1, 11, and 19 respectively to one where the liquid preparations satisfy specific requirements of the preservative efficacy standard of EP-criteria B of the European Pharmacopoeia. The combination of Ogawa and Kapin would lead to a composition which inherently possesses the preservative efficacy claimed in claims 28-30.

Based on the teachings of Ogawa regarding preparation of stable aqueous bromfenac compositions and that tyloxapol is interchangeable with polysorbate 80 as exemplified by Kapin, a person of skill in the art could easily modify the bromfenac compositions described in Examples 6 and 8 of Ogawa to arrive at the compositions and the methods for treating inflammatory eye disease as recited in the claims of the '606 patent with more than a reasonable expectation of success.

2. SECONDARY CONSIDERATIONS

Watson is unaware of any evidence of secondary considerations of non-obviousness of substantive probative value.

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XI. Conclusion

For the reasons discussed herein, each and every claim of U.S. Patent Nos. 8,129,431; 8,669,290; 8,754,131; 8,871,813; and 8,927,606 is invalid, unenforceable and/or not infringed by the commercial manufacture, use or sale of the drug product described in Watson's ANDA.

As such, and as the information provided herein makes clear, there is no reasonable basis for Bausch & Lomb, as the purported holder of approved NDA No. 203168 for Prolensa™

(bromfenac sodium) Ophthalmic Solution, Eq. 0.07% Acid or Senju Pharmaceutical Co., Ltd, as the record owner of U.S. Patent Nos. 8,129,431; 8,669,290; 8,754,131; 8,871,813; and 8,927,606 to institute suit against Watson for filing its ANDA No. 206085.

Watson expressly reserves the right to develop and raise additional noninfringement, invalidity and unenforceability defenses for any or all claims of U.S. Patent Nos. 8,129,431; 8,669,290; 8,754,131; 8,871,813; and 8,927,606.