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SENT BY FEDERAL EXPRESS

December 15, 2014

J. Michael Pearson, CEO
Bausch & Lomb Incorporated
1400 North Goodman Street
Rochester, NY 14609

Yukoh Yoshida, President & CEO
Senju Pharmaceutical Co., Ltd.
2-5-8, Hirano-machi, Chuo-ku
Osaka, Japan

Re: Paragraph IV certifications, notice letter, and offer of confidential access for Bromfenac Sodium Ophthalmic Solution/Drops EQ 0.07% Acid, Paddock Laboratories, LLC ANDA No. 207584.

Dear Sir:

I am writing to inform you that Paddock Laboratories, LLC ("Paddock") has submitted an abbreviated new drug application to the United States Food and Drug Administration (FDA) containing one or more "paragraph IV" certifications in order to obtain approval to engage in the commercial manufacture, use, or sale of bromfenac sodium ophthalmic solution/drops, EQ 0.07% acid ("the Paddock product").

Paddock's abbreviated new drug application ("Paddock's ANDA" or "the application") was submitted pursuant to 21 U.S.C. § 355(j) and received by the FDA. Paddock's ANDA contains any required bioavailability or bioequivalence data or information.

Paddock's ANDA has been assigned No. 207584.

The established name of the drug product is bromfenac sodium ophthalmic solution/drops. The active ingredient, strength, and dosage forms of the proposed drug product are: bromfenac sodium EQ 0.07% acid, ophthalmic solution/drops.

The application included certifications under § 355(j)(2)(A)(vii)(IV) for United States Patent No. 8,129,431 ("the '431 patent"), United States Patent No. 8,669,290 ("the '290 patent"), United States Patent No. 8,754,131 ("the '131 patent") and United States Patent No. 8,871,813 ("the '813 patent"). Paddock has certified that in its opinion and to the best of its knowledge, the claims of the '431, '290, '131 and '813 patents will not be infringed by Paddock's proposed manufacture, use, or sale of its product that is the subject of its application, and/or those claims are invalid or unenforceable. According to Bausch and Lomb's entry in the FDA's electronic Orange Book, the '431 patent expires September 11, 2025, the '290 patent expires January 16, 2024, the '131 patent expires January 16, 2024, and the '813 patent expires on January 16, 2024.

As required by 21 U.S.C. § 355(j)(2)(B)(ii), a detailed statement of the factual and legal bases for Paddock's opinion is set forth below. Furthermore, this enclosure also contains an offer of confidential access pursuant to 21 U.S.C. § 355(j)(5)(C)(iii).

Pursuant to 21 C.F.R. § 314.95(e), Paddock requested and received from the FDA permission to send this notice to the NDA holder and patent owner by means other than registered or certified mail. The FDA granted Paddock's request prior to this notice being sent.

The name and address of an agent authorized to accept service of process for Paddock is:

Shane A. Brunner, Edward J. Pardon, Jeffrey S. Ward, or Wendy M. Ward
Merchant & Gould PC
10 E. Doty Street, Suite 600
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DETAILED STATEMENT

I. Legal Standards

General legal standards utilized here are discussed below. More detailed law is discussed in the analysis sections as needed.

A. Claim Construction

The first step in an infringement or invalidity analysis is to construe the claims. Claim construction is an issue of law, performed by the court, even in a jury trial. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 979 (Fed. Cir. 1995), *aff'd*, 517 U.S. 370 (1996). The interpretation to be given a claim is formed by the

claim language itself, the language of the other claims in the patent, the specification of the patent, the prior art, and the prosecution history. *SRI Int'l v. Matsushita Elec. Corp.*, 775 F.2d 1107, 1118 (Fed. Cir. 1985). Claim terms are generally given their ordinary and established meanings to one of ordinary skill in the art. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312-13 (Fed. Cir. 2005).

The specification is the primary basis for construing the claims, because that is where the inventor provides a full and exact description of the invention. *Phillips*, 415 F.3d at 1315-17. The claims themselves, both asserted and unasserted, are also a valuable source with respect to claim construction. *Id.* at 1314. The prosecution history should also be consulted. *Id.* at 1317. Review of the prosecution history can reveal whether there are any express limitations made regarding the scope and meaning of the claims. *Bell Atlantic Network Servs., Inc. v. Covad Commc'ns Group, Inc.*, 262 F.3d 1258, 1268 (Fed. Cir. 2001). In addition, extrinsic evidence such as dictionaries, technical treatises, articles that are publicly available at the time the patent issued, and expert testimony may also be considered, but this evidence is less significant than the patent itself and its prosecution history. *Phillips*, 415 F.3d at 1317-19.

B. Infringement

After the claim is interpreted, it must be compared to the accused device or process to determine whether the claim's scope encompasses the accused device or process. *North Am. Vaccine, Inc. v. American Cyanamid Co.*, 7 F.3d 1571, 1574 (Fed. Cir. 1993). If the properly interpreted terms of the claim read on the accused device or process, literal infringement is established. *Morton Int'l, Inc. v. Cardinal Chem. Co.*, 5 F.3d 1464, 1468 (Fed. Cir. 1993). Because each element of a claim is material and essential, the patent owner must show the presence of each and every element in the accused device to establish literal infringement. *Charles Greiner & Co. v. Mari-Med Mfg., Inc.*, 962 F.2d 1031, 1034 (Fed. Cir. 1992). The patentee has the burden to show infringement by a preponderance of the evidence. *SmithKline Diagnostics, Inc. v. Helena Laboratories Corp.*, 859 F. 2d 878, 889 (Fed. Cir. 1988).

Absent literal infringement, a legal doctrine termed the doctrine of equivalents may apply to bring an accused device or process under the web of infringement. *Hughes Aircraft Co. v. United States*, 717 F.2d 1351, 1361 (Fed. Cir. 1983). Under the doctrine of equivalents, a patent owner may be successful in an infringement action, even if the claims are not literally infringed, if "the accused product or process contain[s] elements identical or equivalent to each claimed element of the patented invention." *Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 40 (1997). In applying the doctrine of equivalents, one considers

if the differences between the claimed structure or process and the accused device or process are insubstantial from the vantage point of one of ordinary skill in the relevant art. *Hilton Davis Chem. Co. v. Warner-Jenkinson Co.*, 62 F.3d 1512, 1517-18 (Fed. Cir. 1995), *rev'd on other grounds and remanded*, 520 U.S. 17 (1997). It is often enough to assess whether the accused device or process performs substantially the same function in substantially the same way to obtain substantially the same result as the claim element(s) missing from the accused structure or process under the literal infringement analysis. *Hilton Davis*, 62 F.3d at 1518. Furthermore, a patent owner must show the presence of every element or its substantial equivalent in the accused device or process to prove infringement under the doctrine of equivalents. *Pennwalt Corp. v. Durand-Wayland, Inc.*, 833 F.2d 931, 935 (Fed. Cir. 1987).

Application of the doctrine of equivalents can be precluded in certain situations as a matter of law. For example, a patent owner cannot obtain, under the doctrine of equivalents, coverage that could not lawfully have been obtained from the USPTO by literal claims. *Pennwalt*, 833 F.2d at 938. In other words, a claim cannot be read to cover an accused device under the doctrine of equivalents if that claim would then be unpatentable in view of prior art. *Wilson Sporting Goods Co. v. David Geoffrey and Assocs.*, 904 F.2d 677, 684 (Fed. Cir. 1990). In addition, a patentee is precluded from capturing subject matter under the doctrine of equivalents that was disclosed in the patent specification but not claimed by the patentee. *Johnson & Johnston Assocs., Inc. v. R.E. Serv. Co.*, 285 F.3d 1046 (Fed. Cir. 2002) (en banc). Furthermore, a patentee cannot assert the doctrine of equivalents where to do so would "vitiate" or completely read a limitation out of a claim. *Warner-Jenkinson Co.*, 520 U.S. at 39 n.8; *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 469 F.3d 1005, 1017 (Fed. Cir. 2006).

Where an accused activity does not include particular limitations of an independent claim or their substantial equivalents, it follows that, for the same reason, the dependent claims will not be infringed. *Jeneric/Pentron, Inc. v. Dillon Co.*, 205 F.3d 1377, 1383 (Fed. Cir. 2000) ("dependent claims cannot be found infringed unless the claims from which they depend have been found to have been infringed") (citation omitted).

C. Obviousness

A claimed invention in an issued patent is invalid if it would have been obvious to one of ordinary skill in the art at the time the invention was made when viewed in light of the prior art. 35 U.S.C. § 103. Obviousness is a question of law, based on underlying fact issues. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966). These fact issues are: (1) the scope and content of the prior art; (2) the

differences between the claimed invention and the prior art; (3) the level of ordinary skill in the art; and (4) secondary considerations, including unexpected results and commercial success. *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 406 (2007).

To prove obviousness based on a combination of references, it can be helpful to identify whether there must be some reason to combine those references. *KSR*, 550 U.S. at 418-19. The reason to combine references can be provided by any need or problem that is known in the field of endeavor at the time of the invention and addressed by the patent at issue. *Id.* at 420. In addition, where there is a need to solve a problem, and there are a finite number of identified, predictable solutions, a person of ordinary skill in the art has good reason to pursue those solutions. If this leads to anticipated success, it is likely the product of ordinary skill and common sense, and is not inventive. *Id.* at 421.

II. Description of the '431 Patent

A. Background

The '431 patent is entitled "Aqueous Liquid Preparation Containing 2-Amino-3(4-Bromobenzoyl)Phenylacetic Acid." The patent issued on March 6, 2012 from U.S. application No. 10/525,006 ("the '006 application"). The '006 application was the U.S. national phase of PCT application PCT/JP2004/000350, filed on January 16, 2004. The PCT application claimed priority to a Japanese patent application filed on January 21, 2003. The '431 patent lists Shirou Sawa and Shuhei Fujita as inventors. It is assigned to Senju Pharmaceutical Co., Ltd. ("Senju"). The '431 patent expires September 11, 2025, according to the entry in the Orange Book.

B. Claims

The '431 patent contains twenty-two claims, two of which are independent: claims 1 and 18. These claims are reproduced below.

> 1. An aqueous liquid preparation consisting essentially of the following two components, where the first component is [bromfenac] or a pharmaceutically acceptable salt or a hydrate thereof, where the hydrate is at least one selected from a ½ 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.

18. An aqueous liquid preparation consisting essentially of:

(a) [bromfenac] or a pharmaceutically acceptable salt or a hydrate thereof, where the hydrate is at least one selected from a ½ 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.

Claims 2-17 are ultimately dependent on claim 1. Claim 2 requires that bromfenac sodium be used, while claim 3 limits the tyloxapol concentration and the bromfenac sodium concentration to from about 0.01 w/v% to about 0.5 w/v%. Claims 4 and 5 further limit the bromfenac sodium concentration, while claim 6 specifies that the tyloxapol concentration is about 0.02 w/v%. Claim 7 states that the formulation further includes one or more additives selected from certain excipient groups, while claim 8 specifies a single excipient from each group. Claims 9 and 10 are dependent on claim 8, and specify certain pH ranges. Claim 11 is dependent on claim 4, and specifies that the concentration of the bromfenac sodium is about 0.02%, while claim 12 is also dependent on claim 4, and requires the tyloxapol concentration to be about 0.3 w/v%. Claims 13-17 are dependent on claims 12, 13, 11, 15 and 16, respectively, and relate to the presence of further excipients (claims 13, 14, 16 and 17) or a specific tyloxapol concentration (claim 15).

Claims 19-20 are ultimately dependent on claim 18, and require bromfenac sodium (claim 19), and that the bromfenac sodium and tyloxapol concentrations are from about 0.01 w/v% to about 0.5 w/v% and about 0.02 w/v%, respectively. Claims 21 and 22 are also ultimately dependent on claim 18, and require that the bromfenac sodium concentration is about 0.01 w/v% and about 0.1 w/v%, respectively.

C. Specification

The '431 patent specification states that benzalkonium chloride and other quaternary ammonium compounds are generally considered to be incompatible with ophthalmic drug compositions with acidic groups, such as nonsteroidal anti-inflammatory drugs (NSAIDs), because the preservatives form complexes with the drug compounds and lose their ability to function. ('431 patent at col. 1, l. 62 – col. 2, l. 3.) Accordingly, the specification states that it is an object of the invention to provide an aqueous liquid preparation comprising bromfenac or a salt or hydrate thereof that is stable within a pH range that is not irritating to the eye and when a preservative such as benzalkonium chloride is used, the preservative effect of that compound does not substantially deteriorate. (*Id.* at col. 2, ll. 14-22.)

The specification then claims that the inventors have discovered that by adding an alkyl aryl polyether alcohol type polymer such as tyloxapol or a polyethylene glycol fatty acid ester such as polyethylene glycol monostearate to an aqueous liquid preparation comprising bromfenac or its salts or hydrates, the preparation is stable in a non-irritating pH range. (*Id.* at col. 2, ll. 34-43.) The specification also states that in this preparation, the change in bromfenac over time can be inhibited, and where the preparation contains a preservative, the deterioration of the preservative can also be inhibited for a long period of time. ('431 patent at col. 2, ll. 43-49.)

The specification contains several Examples. In Experimental Example 1, various aqueous preparations containing bromfenac sodium and other excipients, including benzalkonium chloride and one of polysorbate 80, tyloxapol, or polyoxyl 40 stearate (a polyethylene glycol monostearate) were tested for stability at 60°C at pH 7 for four weeks. According to the specification, the preparations containing tyloxapol were the most stable, the preparation with polyoxyl 40 stearate was the second most stable, and the preparation with polysorbate 80 was the least stable. (*Id.*at col. 7, ll. 10-64.) The inventors also concluded that the preparation containing 0.02 w/v% tyloxapol was more stable than that containing 0.15 w/v% tyloxapol. (*Id.* at col. 7, l. 65 – col. 8, l. 2.)[1]

[1] The preparations containing polysorbate 80 contained it in a concentration of 0.15 w/v%, while the preparation containing polyoxyl 40 stearate also contained that compound in a concentration of 0.15 w/v%.

Experimental Example 2 tested the stability of various liquid preparations containing bromfenac sodium and other excipients, including benzalkonium chloride and one of tyloxapol or polyoxyl 40 stearate for four weeks at 60°C and a pH of about 8.15. Varying amounts of tyloxapol (0.02 g, 0.03 g, or 0.05 g)[2] or polyoxyl 40 stearate (0.02 g or 0.05 g) were used. The specification stated that all of the preparations had more than 90% of the bromfenac remaining at the end of the test, which indicates that compositions have sufficient stability for eye drops.

Experimental Example 3 tested the preservative effect of three liquid preparations from Experimental Example 2. Two of the preparations contained 0.02 w/v% or 0.05 w/v% tyloxapol, while the other contained 0.02 w/v% polyoxyl 40 stearate. The specification states that these results showed that the preparations met various EP preservative criteria. ('431 patent at col. 8, l. 51 – col. 9, l. 52.)

The specification also contains three example eye drop preparations, all of which contain bromfenac sodium, benzalkonium chloride and other excipients, and one of tyloxapol or polyoxyl 40 stearate. (*Id.* at col. 10, l. 51 – col. 11, l. 43.)

D. Prosecution history

The '006 application as originally filed contained eighteen claims. Claims 1-14 related to aqueous liquid preparations, with claim 1 being the only independent claim in that group. It claimed "[a]n aqueous liquid preparation comprising [bromfenac] or a pharmacologically acceptable salt or hydrate thereof, and an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester." Claims 15 and 16 were both independent and claimed an eye drop comprising bromfenac sodium and either 0.01 to 0.5 w/v% tyloxapol (claim 15) or 0.02 to 0.1 w/v% polyethylene glycol monostearate (claim 16). Claims 17 and 18 were also both independent and related to a method for stabilizing bromfenac or its salts for hydrates by incorporating tyloxapol or polyethylene glycol monostearate (claim 17) or a method for inhibiting the decrease in preservative effect of a preservative in an aqueous liquid preparation of bromfenac or its salts or hydrated by incorporating tyloxapol or polyethylene glycol monostearate.

These claims were then cancelled in a preliminary amendment, and new claims 19-40 were added. Claim 19 was identical to original claim 1, and the only

[2] According to the specification, these amounts equate to w/v%, e.g., 0.02 g tyloxapol is equal to 0.02 w/v% tyloxapol.

other independent claims, claims 39 and 40, were similar to original claims 17 and 18, respectively.

In response to a restriction requirement, the applicants elected claims 19-38. These claims were rejected as being anticipated and obvious. With respect to the obviousness rejections, various claim combinations were rejected over (1) WO 01/15677 to Gamache et al. ("Gamache") in view of publicly available information regarding Xibrom or Nolan, Agents and Actions, 1988 Aug; 25(1-2):77-85, abstract ("Nolan"), (2) "New Drugs in Japan," 2001 and U.S. Patent No. 6,369,112 to Xia ("Xia"), or (3) New Drugs in Japan and Xia in view of Nolan.

The applicants subsequently conducted an interview with the examiner and discussed the various prior art references listed above. Shortly thereafter, on March 26, 2008, the applicants submitted an amendment. There, they amended the claims to require two components, the first being bromfenac or a salt thereof, and the second being an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester. Certain claims specified tyloxapol as the alkyl aryl polyether alcohol type polymer as well as various concentration ranges of the two components.

The applicants also added new claims 41-63. Claims 41-60 tracked claims 19-38, except the new claims contained the phrase "consisting essentially of" instead of "comprising." New claims 61-62 related to a method for stabilizing bromfenac or its salts or hydrates claim (claim 61) or a method for inhibiting decrease in preservative effect of a preservative (claim 62) comprising incorporating tyloxapol or polyethylene glycol monostearate, to obtain a composition consisting essentially of those two components. New claim 63 was similar to claim 19, used the phrase "consisting of" and added optional components.

Addressing the obviousness rejections, the applicants argued that Gamache discloses 5-HT agonist compositions with a great number of other possible ingredients, and does therefore not suggest the claimed composition. The applicants also argued that the presence of the 5-HT agonist was beyond the scope of the claims having the "consisting essentially of" language. With respect to the publicly available information regarding Xibrom, the applicants stated Xibrom has a different composition from that claimed, in that it does not include the required alkyl aryl polyether alcohol type polymer or polyethylene glycol fatty acid ester. They also argued that Nolan also does not disclose this component. Regarding "New Drugs in Japan," the applicants provided a complete translation and argued that it did not teach the use of tyloxapol. The

applicants also contended that Xia was not relevant, because it relates to adding a biguanide to a contact lens solution containing tyloxapol.

The examiner issued another Office Action on July 18, 2008. There, claims 61 and 62 were withdrawn, and the rejections based on Gamache were maintained. The rejections based primarily on "New Drugs in Japan" were not maintained, but the examiner made a new obviousness rejection based on U.S. Patent No. 5,998,465 to Hellberg ("Hellberg") in view of Nolan.

The applicants responded on January 15, 2009. There, they amended claims 19, 41 and 63 to require that the claimed liquid preparation be in the form of an eye drop. They then again argued that Gamache did not disclose or suggest the specific combination of bromfenac or its salts or hydrates in combination with an alkyl aryl polyether alcohol type polymer or polyethylene glycol fatty acid ester. To the extent that Gamache did disclose the use of tyloxapol with a 5-HT agonist, the applicants contended that there was no explanation why it was added to the exemplified composition. The applicants also argued that Gamache did not disclose eye drops.

With respect to the rejection based on Hellberg, the applicants stated that Hellberg related to compositions having anti-inflammatory and antioxidant activity, and that the active agent, unlike bromfenac, had to have both properties. As a result, the applicants contended, substitution of bromfenac in the Hellberg compositions would render those compositions unsatisfactory for their intended purpose.

A new examiner issued an Office Action on June 3, 2009, and again rejected all of the pending claims. The examiner maintained the rejections based on Gamache and Hellberg, and made them final.

The applicants then submitted a Request for Continuing Examination ("RCE") on October 5, 2009. There, they amended claims 19, 41 and 63 to remove the language that the compositions be in the form of an eye drop, and instead added language that the compositions be formulated for ophthalmic administration. This amendment had been suggested by the examiner in the previous Office Action. Shortly thereafter, the applicants conducted an interview with the examiner and again asserted that there would be no motivation to use bromfenac in the Hellberg compositions.

The examiner issued another Office Action on December 24, 2009. There, she maintained the previous rejections. The applicants then had another interview with the examiner, and explained that the tyloxapol in Hellberg was not used as a cosolvent. They then submitted an amendment on March 24, 2010.

There, they cancelled claims 19-40 and 63, among others, leaving the "consisting essentially of" claims in issue. They also added new claims 64-68. Claim 64 was independent and specified that the claimed aqueous liquid preparation consist essentially of bromfenac or a salt or hydrate, tyloxapol, boric acid, sodium tetraborate, EDTA sodium salt, benzalkonium chloride, polyvinylpyrrolidone, and sodium sulfite, where it is formulated for ophthalmic administration. The applicants then stated that the examiner had agreed to withdraw the rejection based on Gamache, and that there was no motivation to replace the bifunctional compounds of Hellberg with bromfenac.

The examiner responded on June 24, 2010. There, she rejected the claims as anticipated by U.S. Patent No. 5,603,929 to Desai ("Desai") and obvious over Desai in view of U.S. Patent No. 5,475,034 to Yanni ("Yanni") and Hellberg. She again made the rejection final.

The applicants then submitted a second RCE on October 25, 2010. There, the applicants amended claims 41 and 64 to require that when a quaternary ammonium compound is added to the claimed liquid preparation, it is benzalkonium chloride. The applicants then argued that Desai disclosed using polymeric quaternary ammonium compounds as preservatives and taught that benzalkonium chloride is incompatible with NSAIDs, because the benzalkonium chloride forms complexes with the charged drug compounds and loses its ability to function as a preservative. As a result, the applicants argued that Desai taught away from the claimed formulations, which require the use of benzalkonium chloride if a quaternary ammonium compound is used.

The applicants further discussed this issue with the examiner in an interview held on January 14, 2011. In response, the examiner issued an Office Action on May 6, 2011. There, she withdrew the rejection based on Desai, but rejected the pending claims over Yanni in view of U.S. Patent No. 5,540,930 to Guy ("Guy") and in some instances in further view of Gamache.

The applicants responded on September 6, 2011. There, they contended that Yanni did not disclose bromfenac, but instead disclosed an amide derivative in combination with polysorbate 80, and that Yanni was not directed to the use of bromfenac. The applicants also argued that Guy did not teach the equivalency of tyloxapol and polysorbate 80, as it was directed to a different problem, and in addition, that as shown in applicants' application, tyloxapol was unexpectedly superior as a stabilizer to polysorbate 80 in a bromfenac composition subjected to stability testing at pH 7.0 at 60°C for four weeks.

The examiner was not convinced, and maintained the rejections in an Office Action dated November 15, 2011. The rejection was again made final.

However, inexplicably, on December 23, 2011, the examiner reversed course and issued a Notice of Allowance. The examiner stated that the prior art did not teach or suggest the claimed liquid preparations, and that the applicants had discovered that tyloxapol was not equivalent to polysorbate 80 when combined with bromfenac, based on the information in the specification. The examiner also stated that Desai taught that only polymeric quaternary ammonium compounds should be used with bromfenac, while the amended claims require that the quaternary ammonium compound be benzalkonium chloride.

The '431 patent then issued on March 6, 2012.

III. Claims 1-10, 18-20 and 22 of the '431 Patent are Invalid as Obvious

Claims 1-10, 18-20 and 22 of the '431 patent are invalid under § 103 as obvious over U.S. Patent No. 4,910,225 ("the '225 patent") or New Drugs in Japan in view of U.S Patent No. 6,107,343 ("the '343 patent"), U.S. Patent No. 5,457,126 ("the '126 patent"), European Patent No. 0443766 ("EP '766"), U.S. Patent No. 6,274,609 ("the '609 patent") and/or Guy. The '225 patent discloses bromfenac ophthalmic compositions including benzalkonium chloride and polysorbate 80, as well as other components. New Drugs in Japan discloses an approved ophthalmic composition containing bromfenac sodium hydrate, along with polysorbate 80 and benzalkonium chloride. The '343 patent, the '126 patent and EP '766 disclose the use of tyloxapol with drug substances (including NSAIDs) having acidic groups in combination with quaternary ammonium compounds, such as benzalkonium chloride, and the '609 patent and Guy disclose the substitutability of tyloxapol for polysorbate 80 in ophthalmic compositions and the benefits thereof, including improved stability and antimicrobial effect.

Accordingly, one of ordinary skill in the art would have understood that the polysorbate 80 in the bromfenac formulations of the '225 patent or New Drugs in Japan could be replaced with tyloxapol, and would have had a reasonable expectation of success that the resulting product would be stable, sterile and useful for ophthalmic administration. Further, while Senju argued that bromfenac compositions containing tyloxapol were unexpectedly more stable than those containing polysorbate 80, the alleged evidence of unexpected result is insufficient to render the claims non-obvious, when all four *Graham* factors are considered together. This conclusion is explained in more detail below.

A. Claim Construction

Here, the claims will be construed in accordance with their ordinary meaning to one of ordinary skill in the art. For the purposes of this notice letter, there are no claim terms needing further construction.

B. The Scope and Content of the Prior Art

The '225 patent discloses ophthalmic compositions for use in treating inflammatory eye diseases. Specifically, Examples 6 and 8 disclose ophthalmic solutions containing bromfenac sodium monohydrate as the active ingredient, along with other components, including polysorbate 80 and benzalkonium chloride, where the composition has a pH of 8. ('225 patent at col. 10, ll. 4-17; col. 10, ll. 35-48.) The '225 patent also discloses that these compositions were "stable, excellent for a long period of time." (*Id.* at col. 10, ll. 50-57.)

Likewise, New Drugs in Japan also discloses an approved ophthalmic composition for use in treating inflammatory eye diseases. The composition, trade named Bronuck, contains bromfenac (0.1%) as bromfenac sodium sesquihydrate, along with other components, including polysorbate 80 and benzalkonium chloride. One of ordinary skill in the art would understand that this product is both sterile and stable for a pharmaceutically acceptable amount of time—otherwise it would not have been approved.

The '343 patent discloses ophthalmic compositions comprising diclofenac potassium (a NSAID) for the treatment of inflammatory conditions of the eye. ('343 patent at col. 1, ll. 8-11.) It also discloses that the composition can contain a solubilizer and a preservative, with one of the preferred solubilizers being tyloxapol and one of the preferred preservatives being benzalkonium chloride. (*Id.* at col. 4, ll. 52-67; col. 5, ll. 28-38.) Finally, in Example 2, the '343 patent discloses an eye drop formulation comprising diclofenac potassium, tyloxapol, and benzalkonium chloride. (*Id.* at col. 8, ll. 1-15.)

The '126 patent discloses ophthalmic compositions for the treatment of ocular allergic responses, including inflammation, such as from conjunctivitis. Specifically, it discloses ophthalmic formulations containing lodoxamide tromethamine, which is a phenylene dioxamic acid. ('126 patent at col. 1, ll. 14-43; col. 2, ll. 39-49.) The formulations also contain tyloxapol and benzalkonium chloride, among other excipients. (*Id.* at col. 2, ll. 39-49.)

EP '766 relates to ophthalmic compositions comprising an antiallergic compound, such as lodoxamide, and an antihistamine. The compositions can also contain a preservative, such as benzalkonium chloride, as well as other components. (EP '766 at 3.) EP '766 provides an example formulation containing

lodoxamide tromethamine and pheniramine maleate as active agents, as well as tyloxapol and benzalkonium chloride, among other things. (*Id.* at 4.)

The '609 patent discloses aqueous solutions, including eye drops, that contain pranlukast as the active ingredient. The '609 patent discloses that tyloxapol is a good solubilizing agent for pranlukast. ('609 patent at col. 4, l. 55 – col. 5, l. 32.) It also discloses that a pranlukast aqueous solution containing tyloxapol and benzalkonium chloride (formulation A) had superior stability to a formulation containing polysorbate 80 and either no preservative or the stabilizer EDTA or BHT (formulations D, E and F). (*Id.* at col. 6, l. 47 – col. 7, l. 45.)

Guy relates to suspensions for ophthalmic and other uses that contain corticosteroids, such as loteprednol etabonate as an active agent. These formulations contain additional excipients, including surface-active agents and preservatives. (Guy at col. 3, ll. 60-67.) The surface-active agents include both polysorbate 80 and tyloxapol, while the preservative can be benzalkonium chloride. (*Id.* at col. 4, ll. 15-30; col. 4, l. 64 – col. 5, l. 10.) Guy also discloses various loteprednol compositions containing polysorbate (Tween) 80 and/or tyloxapol, along with benzalkonium chloride. (*Id.* at cols. 5-6.) Certain of these formulations were subjected to stability and antimicrobial testing. Guy discloses that various formulations containing polysorbate 80 and tyloxapol were stable. (Guy at col. 7, l. 32 – col. 8, l. 31.) In addition, Guy discloses that compositions containing tyloxapol were superior in preventing antimicrobial growth over time as compared to those containing polysorbate 80. (*Id.* at col. 8, ll. 32-57.)

C. Person of Ordinary Skill in the Art

Here, a person of ordinary skill in the art would have a Ph.D in chemistry, pharmaceutical sciences or a related field, and at least several years of experience in drug product formulation, including ophthalmic compositions.

D. Differences Between the Claimed Invention and the Prior Art

The only feature of the claimed invention not specifically disclosed by the prior art is the combination of bromfenac and tyloxapol in a pharmaceutical composition for ophthalmic use. Specifically, the '225 patent and New Drugs in Japan disclose each of the limitations of claims 1-10, 18-20 and 22, but for tyloxapol. However, the '126 patent and EP '766 do disclose the use of tyloxapol with acidic ophthalmic agents, in combination with benzalkonium chloride. The amount of tyloxapol present in the formulations of these two references, 0.025%, is within the specific tyloxapol ranges of claims 3, 4, and 6, and is sufficiently close to the "about 0.02%" of claim 20. As a result, claims 1-10, 18-20 and 22 would have been obvious.

First, the '225 patent and New Drugs in Japan disclose bromfenac ophthalmic compositions for treating inflammatory diseases, where the compositions contain 0.1g/100 ml (0.1%) bromfenac, along with polysorbate 80 and benzalkonium chloride. One of ordinary skill in the art would understand from these disclosures that bromfenac could be formulated with both polysorbate 80 and benzalkonium chloride without the formation of complexes that would make the formulation less stable.

Second, one of ordinary skill in the art would understand from the '343 patent, the '126 patent and EP '766 that tyloxapol could also be used in ophthalmic formulations containing an active agent with acidic groups (diclofenac and lodoxamide), again in combination with benzalkonium chloride. In this regard, it also would have been understood that tyloxapol was a preferred solubilizer for diclofenac. Thus, one of ordinary skill in the art would have known that tyloxapol would also not form deleterious complexes when used with acidic active agents, including the NSAID diclofenac, and benzalkonium chloride, and that it was a preferred solubilizer.

Further, one of ordinary skill would have known that tyloxapol had already been approved for use by the FDA, and was present in both brinzolamide ophthalmic suspension (Azopt) and tobramycin/dexamethasone ophthalmic suspension (Tobradex), two prior art products. In addition, tyloxapol was one of only a handful of non-ionic surfactants (along with polysorbate 80, octoxynol 80 and polyoxyl 40 hydrogenated castor oil) in use in ophthalmic products as of 2003, according to the Physician's Desk Reference.

Additionally, one of ordinary skill in the art would have known from the '609 patent that an aqueous formulation containing tyloxapol was more stable that one containing polysorbate 80.

Finally, one of ordinary skill in the art would have known from Guy that polysorbate 80 and tyloxapol can provide stable ophthalmic formulations. In addition, such a person would have understood that compositions containing tyloxapol showed better antimicrobial preservative effect than those containing polysorbate 80.

As a result, one of ordinary skill in the art would understand that replacing the polysorbate 80 with tyloxapol in the formulations disclosed in the '225 patent and New Drugs in Japan would likely result in a stable bromfenac composition, with potentially improved antimicrobial preservative effect. Such a person would thus be motivated to make this replacement, given the disclosure of the '343 patent, the '609 patent and Guy, and the fact that tyloxapol was part of a very small group of non-ionic surfactants used in approved ophthalmic

products. Also, that person would have had a reasonable expectation of success, in view of the above information.

E. Objective Evidence of Non-Obviousness

During prosecution of the '431 patent, Senju argued that tyloxapol was an unexpectedly better stabilizer than polysorbate 80 with respect to bromfenac aqueous solutions, citing to Experimental Example 1 and Table 1. (Amendment dated September 6, 2011 at 7-8.) These alleged unexpected results, however, when considered together with the other *Graham* factors, do not result in claims 1-10, 18-20 and 22 being non-obvious.

First, the tests in Experimental Example 1 at most show a difference in degree of stability depending on whether polysorbate or tyloxapol was used, as opposed to a difference in kind. Accordingly, this is not an unexpected result. *Galderma Laboratories L.P. v. Tolmar Inc.*, 737 F.3d 731, 739 (Fed. Cir. 2013).

Second, compositions containing polysorbate 80 were not tested under the same conditions as those containing tyloxapol with respect to polysorbate 80 concentration, pH and the presence of additional excipients. If the polysorbate 80 compositions were adjusted to match the compositions containing tyloxapol, it is likely that the stability results would be substantially similar.

In addition, any alleged superiority for tyloxapol over polysorbate 80 is not unexpected, given the disclosure in the '609 patent and Guy. As stated above, the '609 patent discloses that aqueous solutions containing tyloxapol were more stable than those containing polysorbate 80, and Guy discloses that the substitution of tyloxapol for polysorbate 80 results in improved antimicrobial efficacy.

Therefore, the alleged unexpected results alleged by Senju during the prosecution of the '431 patent are extremely weak to non-existent.

F. Conclusion on Obviousness

Considering all of the *Graham* factors together, claims 1-10, 18-20 and 22 are invalid under § 103 as obvious.

IV. Paddock's ANDA Product Would Not Infringe Claims 11-17 and 21 of the '431 Patent

Each ml of Paddock's product, among other things, will contain 0.0805% bromfenac sodium sesquihydrate, which is equivalent to 0.07% bromfenac free acid. It will also contain significantly less than 0.3% tyloxapol. Claim 11 requires that the claimed preparation contain 0.2% bromfenac sodium, while claim 12 requires the presence of 0.3% tyloxapol. Therefore, these claims will not be

literally infringed by Paddock's product. Nor will infringement under the doctrine of equivalents be present, as the amounts of bromfenac sodium and tyloxapol in Paddock's product are significantly different from the claimed amounts.

Claims 13-17 are dependent on one or more of these claims, and therefore will not be infringed either.

Finally, claim 21 requires the presence of 0.01% bromfenac sodium. As Paddock's product will contain substantially more bromfenac sodium than the claimed amount, there would be no infringement, either literally or under the doctrine of equivalents.

Therefore, Paddock's product will not infringe claims 11-17 and 21[3] of the '431 patent.[4]

V. Description of the '290 Patent

A. Background

The '290 patent is entitled "Aqueous Liquid Preparation Containing 2-Amino-3(4-Bromobenzoyl)Phenylacetic Acid"and issued on March 11, 2014, from U.S. application No. 13/687,242 ("the '242 application"), which was filed on November 18, 2012 as a divisional of U.S. Application No. 13/353,653 ("the '653 application"). The '653 application was filed on January 19, 2012 as a divisional of the '006 application. The '290 patent lists Shirou Sawa and Shuhei Fujita as inventors. It is assigned to Senju Pharmaceutical Co., Ltd. ("Senju"). The '290 patent expires January 16, 2024, according to the entry in the Orange Book.

B. Claims

The '290 patent contains thirty claims, of which three claims (claims 1, 8 and 14) are independent. Those claims are reproduced below 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 ½ hydrate, 1

[3] Claims 5 and 22, which require that the concentration of the bromfenac sodium be "about 0.1%" are also not infringed, as 0.0805% is not "about 0.1%."

[4] These claims are also invalid as obvious for the same reasons expressed above with respect to claims 1-10, 18-20 and 22.

> 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.
>
> 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 ½ 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.
>
> 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 ½ 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.

Claims 2-7 and 30 are ultimately dependent on claim 1. Claim 2 requires that the claimed liquid preparation also comprise a quaternary ammonium salt, while claim 3 specifies the use of bromfenac sodium. Claims 4 and 5 relate to the concentration of the tyloxapol and bromfenac sodium in the claimed preparation, while claim 6 specifies a pH range. Claim 7 adds additional excipients, while claim 30 requires one or more additives selected from a general group of excipients.

Claims 9-13 are ultimately dependent on claim 8. Claim 9 requires that the claimed liquid preparation also comprise a quaternary ammonium compound, while claim 10 requires that greater than 92% of the bromfenac remains in the preparation after storage at about 60°C. for four weeks. Claim 11 relates to the

concentration of the tyloxapol and bromfenac sodium in the claimed preparation, while claim 12 specifies a pH range. Claim 13 adds additional excipients.

Claims 15-25 are ultimately dependent on claim 14. Claim 15 requires that the claimed liquid preparation also comprise a quaternary ammonium compound, while claim 16 requires the use of bromfenac sodium. Claim 17 relates to the concentration of the tyloxapol and bromfenac sodium in the claimed preparation, while claim 18 specifies a pH range. Claim 19 adds additional excipients. Claim 20 adds the requirement to claim 14 that greater than 90% of the bromfenac remains in the preparation after storage at about 60°C. for four weeks. Claims 21-25 are ultimately dependent on claim 20, and add the same requirements as claims 2, 10, 4, 6 and 7 respectively.

Claims 25-29 are dependent on claims 1, 4, 7, 9 and 13, respectively, and require that the liquid preparation satisfy particular preservative efficacy standards of the US Pharmacopoeia.

C. The Specification

As the '290 patent is a divisional of a divisional of the '006 application, the specification is the same as that in the '431 patent.

D. Prosecution History

The '653 application was filed with the same original eighteen claims from the '006 application. After a second preliminary amendment, claims 1, 2, 4-14 and 16-27 remained, with claims 1 and 16-18 being independent. Claim 1 specified that the claimed alkyl aryl polyether alcohol type polymer is not tyloxapol. Claims 2, 4-14 and 19-27 were dependent on claim 1. Claims 16-18 read as originally filed in the '006 application. The examiner then issued a restriction requirement between claims 1, 2 4-14, 16 and 19-27 (Group I--aqueous liquid preparations) and claim 17 and 18 (Group II--methods for stabilizing bromfenac). In response, the applicants elected Group I.

The examiner then issued an Office Action on August 30, 2012, rejecting all of the claims in issue for various reasons, including obviousness under § 103. Prior to responding to that Office Action, the applicants filed the '242 application on November 28, 2012.

In the '242 application, the applicants filed a preliminary amendment in which they cancelled claims 1-18, and added new claims 19-48. These claims are substantially identical to issued claims 1-30 of the '290 patent, with the exception that claims 44-48 did not contain the specific viable cell count standards from EP-

criteria B that are recited in issued claims 25-30. The applicants also asked for prioritized examination, which was granted.

On March 25, 2013, the examiner issued a restriction requirement requiring the applicants to select a single species of quaternary ammonium salts. The applicants then elected benzalkonium chloride. On August 1, the examiner issued an Office Action rejecting claims 44-48 as indefinite with reference to EP-criteria B. The examiner then rejected all of the pending claims as obvious under § 103 on one or more of the following grounds: (1) Gamache; (2) Gamache in view of Desai, and (3) Gamache in view of the '225 patent and U.S. Patent No. 6,162,393 ("the '393 patent"). The claims were also rejected for obviousness-type double patenting over U.S. Patent No. 7,829,544, the '431 patent, and two copending applications.

The applicants responded on October 22, 2013. There, they amended claims 19, 27 and 32 to require that bromfenac be the sole active agent in the formulation, amended claims 44-48 to add the viable cell count criteria of EP-criteria B, and made other minor amendments. With respect to the obviousness rejection over Gamache, the applicants stated that Gamache taught compositions containing a 5-HT receptor agonist, and thus could not teach a formulation having bromfenac as the sole active agent. The applicants also argued that Gamache did not teach the limitation in certain claims that greater than 90% of the bromfenac remain after storage at 60°C for four weeks. They stated that Gamache did not recognize "that bromfenac degrades rapidly in the presence of polysorbate 80," and that applicants recognized this problem and solved it by the use of tyloxapol. (Amendment dated October 22, 2013 at 10-11.)

With respect to the rejection based on Gamache in view of Desai, the applicants merely argued that this rejection was not proper, since Gamache did not disclose bromfenac as the sole active agent. Turning to the rejection based on Gamache in view of the '225 patent and the '393 patent, the applicants again argued that Gamache did not teach bromfenac as the sole active agent. They also argued that the claims relating to the amount of bromfenac remaining upon storage were non-obvious for the same reason set forth above with respect to Gamache alone.

The applicants also filed terminal disclaimers to overcome the obviousness-type double patenting rejections.

After an interview with the examiner, the examiner issued a Notice of Allowance on February 11, 2014. There, the examiner amended claims 26 and 27 to require that bromfenac be the sole active agent in the formulation. The examiner then stated that the claims were allowable over a prior art reference to

Chen cited in the '653 application with respect to claims there directed to the use of polyethylene glycol fatty acid esters, such as polyoxyl 40 stearate, based on unexpected results. As the present claims relate to the use of tyloxapol, the examiner was clearly confused. In any event, the '290 patent then issued on March 11, 2014.

VI. Claims 1-30 of the '290 Patent are Invalid as Obvious

A. Claim Construction

The only claim construction issues necessary to discuss for the purposes of this notice letter relate to (1) the term "stable,", which appears in the independent claims, (2) the clause in claims 8, 10, 20 and 22 regarding the amount of bromfenac remaining in the formulation after storage at 60°C for four weeks, and (3) the clause in claims 25-30 that the claimed liquid preparation satisfy the efficacy standard of EP-criteria B.

For the purposes of this notice letter, the term "stable" will be considered a limitation, even though it appears in the claim preamble. The only stability testing disclosed in the '290 patent is storage testing at 60°C for four weeks. There, the patent states that if after storage under these conditions, a formulation contains not less than 90% bromfenac remaining, that formulation has sufficient stability for use as eye drops. (the '290 patent at col. 8, ll. 39-52.). Thus, "stable" will be construed to mean that a given formulation has at least 90% of its original bromfenac remaining after storage at 60°C for four weeks.

The clause in claims 8 and 20 regarding the amount of bromfenac remaining is merely duplicative of the definition of the term "stable," and thus adds nothing to the claim. The clause in claims 10 and 22 requires that greater than about 92% bromfenac remain after storage. This will be interpreted according to its plain meaning.

Turning to the clause regarding EP-criteria B in claims 26-30, that clause will not be considered a claim limitation. It merely states the necessary consequence of the other affirmative limitations set forth in the claim. Because the clause begins with the word "wherein," it is presumed to merely state the consequences of other limitations already set forth in the claim. *See Israel v. Cresswell*, 166 F.2d 153, 156 (C.C.P.A. 1948) ("In this case, as is presumed to be true in all cases in which the claims have a whereby clause, the clause states the result. The result, of course, is not patentable and when stated it adds nothing to the patentability of a claim."); *Prometheus Labs. Inc. v. Roxane Labs., Inc.*, No. 11-230, 2013 WL 5333033 at *5 (D.N.J. Sept. 23, 2013) (explaining that courts and the USPTO treat "whereby" and "wherein" clauses the same); *see also King Pharms.,*

Inc. v. Eon Labs., Inc., 593 F. Supp. 2d 501, 512 (E.D.N.Y. 2009 (holding that a "wherein" clause is not a limitation "because it merely recites an inherent property").

The specification confirms this is the case. All of the formulations containing tyloxapol in the '290 patent specification meet the requirements of EP-criteria B. Accordingly, this clause will not be considered a claim limitation. *See Minton v. Nat'l Ass'n of Sec. Dealers*, 336 F.3d 1373, 1381 (Fed. Cir. 2003).

B. Obviousness Analysis

Claims 1-30 are invalid under § 103 as obvious for the same reasons set forth with respect to the claims of the '431 patent.[5] The claims of the '290 patent contain the same limitations as those in the '431 patent, with the exception of the term "stable" and the limitations in claims 10 and 22 requiring greater than 92% of the bromfenac originally present to be remaining after storage at 60°C for four weeks.[6] These limitations would have been obvious.

As discussed above, New Drugs in Japan discloses a bromfenac sodium ophthalmic formulation containing all of the excipients set forth in the '290 patent claims, except for tyloxapol. As this formulation was approved for use in Japan, it clearly would meet the stability limitations of the claims, including those in claims 10 and 22. Moreover, as stated above, it would have been obvious to replace the polysorbate 80 in that formulation with tyloxapol, and there are no unexpected results. Accordingly claims 1-30 are invalid as obvious.[7]

VII. Description of the '131 Patent

A. Background

The '290 patent is entitled "Aqueous Liquid Preparation Containing 2-Amino-3(4-Bromobenzoyl)Phenylacetic Acid"and issued on June 17, 2014 from U.S. Application No. 14/165,976 ("the '976 application"), which was filed on

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[5] Claim 5 is also not infringed for the reasons set forth above with respect to claim 5 of the '431 patent.

[6] The claims also require that bromfenac be the sole active agent. This is the case for both the '225 patent and New Drugs in Japan.

[7] Even if the clause regarding EP-criteria B is a claim limitation, that limitation would also be met, as it would be inherent in the formulation from New Drugs in Japan or the '225 patent with tyloxapol replacing the polysorbate 80. *See Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354 (Fed. Cir. 2012).

January 28, 2014, as a divisional of the '242 application, now the '290 patent. The '242 application was filed on November 28, 2012 as a divisional of U.S. Application No. 13/353,653 ("the '653 application"). The '653 application was filed on January 19, 2012 as a divisional of the '006 application, which became the '431 patent. The '131 patent lists Shirou Sawa and Shuhei Fujita as inventors. It is assigned to Senju Pharmaceutical Co., Ltd. ("Senju"). The '131 patent expires January 16, 2024, according to the entry in the Orange Book.

B. The Claims

The '131 patent contains thirty claims, of which three claims (claims 1, 7 and 13) are independent. Those claims 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 ½ 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 wt%; 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.
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> 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 ½ 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 wt%; 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.
>
> 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 ½ 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 wt%; 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; provided that the liquid preparation does not contain mannitol.

Claims 2-6 are ultimately dependent on claim 1. Claim 2 requires that the claimed liquid preparation also comprise a quaternary ammonium salt, while claim 3 specifies the use of bromfenac sodium. Claim 4 relates to the concentration of the tyloxapol in the claimed preparation, while claim 5 specifies a pH range. Claim 6 adds additional excipients.

Claims 8-12 are ultimately dependent on claim 7. Claim 8 requires that the claimed liquid preparation also comprise a quaternary ammonium compound, while claim 9 requires that greater than 92% of the bromfenac remains in the preparation after storage at about 60°C. for four weeks. Claim 10 relates to the concentration of the tyloxapol and bromfenac sodium in the claimed preparation, while claim 11 specifies a pH range. Claim 12 adds additional excipients.

Claims 14-24 are ultimately dependent on claim 13. Claim 14 requires that the claimed liquid preparation also comprise a quaternary ammonium compound, while claim 15 requires the use of bromfenac sodium. Claim 16 relates to the concentration of the tyloxapol and bromfenac sodium in the claimed preparation, while claim 17 specifies a pH range. Claim 18 adds additional excipients. Claim 19 adds the requirement to claim 13 that greater than 90% of the bromfenac remains in the preparation after storage at about 60°C. for four weeks. Claims 20-24 are ultimately dependent on claim 19, and add the same requirements as claims 2, 9, 10, 5 and 6, respectively.

C. The Specification

As the '131 patent is a divisional of the '290 patent, the specification is the same as that in the '290 and '431 patents.

D. The Prosecution History

The '976 application was filed on January 28, 2014. At that same time, the applicants submitted a Preliminary Amendment. There, they cancelled claims 1-18, and added new claims 19-48. These claims became issued claims 1-30 of the '131 patent.

The applicants also filed a request to Track One Priority, which was granted. On March 13, 2014, the examiner issued an Office Action rejecting the pending claims for double-patenting over the '431 patent, the '290 patent, and U.S. Patent No. 8,497,304. The applicants then submitted terminal disclaimers

with respect to each of those patents, and the claims were subsequently allowed on April 21, 2014.

VIII. Claims 1-30 of the '131 Patent are Invalid as Obvious

A. Claim Construction

Any claim term needing construction for the purposes of this notice letter has been previously construed with respect to either the '431 or '290 patents, with the possible exception of the limitation in claims 25-29 that the claimed aqueous preparations meet certain preservative efficacy standards of the US Pharmacopoeia. This will not be considered a claim limitation, for the same reasons expressed above with respect to claims 25-30 of the '290 patent.[8]

B. Obviousness Analysis

Claims 1-30 of the '131 patent are invalid under § 103 as obvious for the same reasons expressed above with respect to the '431 and '290 patents. The claims contain no additional limitations over those discussed with respect to those two patents.[9]

IX. Description of the '813 Patent

A. Background

The '813 patent is entitled "Aqueous Liquid Preparation Containing 2-Amino-3(4-Bromobenzoyl)Phenylacetic Acid"and issued on October 28, 2014 from U.S. Application No. 14/261,720 ("the '720 application"), which was filed on April 25, 2014 as a divisional of the '976 application, now the '131 patent. The '976 application was filed on January 28, 2014, as a divisional of the '242 application, now the '290 patent. The '242 application was filed on November 28, 2012 as a divisional of the '653 application. The '653 application was filed on January 19, 2012 as a divisional of the '006 application which became the '431 patent. The '813 patent lists Shirou Sawa and Shuhei Fujita as inventors. It is

[8] There is no reference in the '131 patent to any U.S. Pharmacopeia standards, and the claim language actually appears to relate to EP Pharmacopoeia Criteria A and B.

[9] Even if the clauses regarding "US Pharmacopoeia" preservative standards in claims 25-29 are claim limitations, those limitations would also be met, as they would be inherent in the formulation from New Drugs in Japan or the '225 patent with tyloxapol replacing the polysorbate 80. *See Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354 (Fed. Cir. 2012).

assigned to Senju Pharmaceutical Co., Ltd. ("Senju"). The '813 patent expires January 16, 2024, according to the entry in the Orange Book.

B. Claims

The '813 patent contains twenty-seven claims, of which three claims (claims 1, 7 and 13) are independent. Those three claims read as follows:

> 1. A stable 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 ½ 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.
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> 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 ½ 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.
>
> 13. 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 ½ 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.

Claims 2-6 are dependent on claim 1. Claim 2 requires that the claimed preparation also contain sodium sulfite, while claim 3 specifies the use of bromfenac sodium. Claim 4 relates to the concentration of the tyloxapol in the claimed preparation, while claim 5 specifies a pH range. Claim 6 adds additional excipients and specifies concentration ranges for the bromfenac sodium and the tyloxapol.

Claims 8-12 are dependent on claim 7. Claim 8 requires that the claimed preparation also contain sodium sulfite, while claim 9 requires that greater than 92% of the bromfenac remains in the preparation after storage at about 60°C. for four weeks. Claim 10 relates to the concentration of the tyloxapol and bromfenac sodium in the claimed preparation, while claim 11 specifies a pH range. Claim 12 adds additional excipients and specifies concentration ranges for the bromfenac sodium and the tyloxapol.

Claims 14-23 are ultimately dependent on claim 13. Claim 14 requires that the claimed liquid preparation further contains sodium sulfite, while claim 15 requires the use of bromfenac sodium. Claim 16 relates to the concentration of the tyloxapol and bromfenac sodium in the claimed preparation, while claim 17 specifies a pH range. Claim 18 adds additional excipients and specifies concentration ranges for the bromfenac sodium and the tyloxapol. Claim 19 adds the requirement to claim 13 that greater than 90% of the bromfenac remains in the preparation after storage at about 60°C. for four weeks. Claims 20-23 are ultimately dependent on claim 19, and add the same requirements as claims 9, 10, 5 and 6, respectively.

Claims 24-26 are dependent on claims 1, 7 and 13, respectively, and require that the claimed preparation does not contain any preservative. Finally, claim 27 is dependent on claim 1, and allows for other excipients to optionally be present.

C. Specification

As the '813 patent is a divisional of the '131 patent, the specification is the same as that in the '131, '290 and '431 patents.

D. Prosecution History

The '720 application was filed on April 25, 2014. At that same time, the applicants submitted a Preliminary Amendment. There, they cancelled claims 1-18, and added new claims 19-45. These claims became issued claims 1-27 of the '813 patent.

The applicants also filed a request to Track One Priority, which was granted. On July 24, 2014, the examiner issued an Office Action rejecting the pending claims for double-patenting over the '431 patent, the '290 patent, the '131 patent and U.S. Patent No. 8,497,304. The applicants then submitted terminal disclaimers with respect to each of those patents, and the claims were subsequently allowed on September 5, 2014. The '813 patent subsequently issued on October 28, 2014.

X. Claims 1-27 of the '813 Patent are Invalid as Obvious

A. Claim Construction

Any claim term needing construction for the purposes of this notice letter has been previously construed above with respect to either the '431 or '290 patents.

B. Obviousness Analysis

Claims 1-27 of the '813 patent are invalid under § 103 as obvious for the same reasons expressed above with respect to the '431 and '290 patents. The claims contain no additional limitations over those discussed with respect to those two patents.

OFFER OF CONFIDENTIAL ACCESS

As referenced under 21 U.S.C. §355 (j)(5)(C)(i)(III), Paddock hereby makes the accompanying Offer of Confidential Access to Bausch & Lomb and Senju concerning relevant portions of Paddock's ANDA No. 207584 for its bromfenac sodium product that is the subject of this notice.

CONCLUSION

For at least the reasons discussed above, claims 1-10, 18-20 and 22 of the '431 patent are invalid as obvious, and claims 11-17 and 21 of that patent would not be infringed by Paddock's product. In addition, claims 1-30 of the '290 patent, claims 1-30 of the '131 patent and claims 1-27 of the '813 patent are also invalid as obvious. Furthermore, we believe that discovery and additional research may very well provide additional grounds for invalidity, unenforceability, and/or non-infringement.

Therefore, we believe that there is no reasonable basis for Bausch & Lomb or Senju to institute suit against Paddock for the filing of Paddock's ANDA containing the foregoing paragraph IV certifications. Moreover, we believe that such a suit would render this case exceptional under 35 U.S.C. § 285, warranting the award of attorney's fees to Paddock.

Please contact the undersigned if you have any questions.

Sincerely,

MERCHANT & GOULD, P.C.

Jeffrey S. Ward

Encl: Offer of Confidential Access

OFFER OF CONFIDENTIAL ACCESS REGARDING ANDA NO. 207584

This Offer of Confidential Access Regarding Abbreviated New Drug Application ("ANDA") No. 207584 (this "Offer") is made on this 15th day of December, 2014 (the "Effective Date") by Paddock Laboratories, LLC ("Company"), to Bausch & Lomb Incorporated and Senju Pharmaceutical Co., Ltd. ("Recipients"), pursuant to 21 U.S.C. §355(j)(5)(C)(i)(III).

WHEREAS, the Company desires to provide to the Recipients certain information relating to Company's bromfenac sodium ophthalmic solution/drops EQ 0.07% acid product that is the subject of ANDA No. 207584 for the purpose of evaluating the possible infringement of United States Patent Nos. 8,129,431 ("the '431 patent"), 8,669,290 ("the '290 patent"), 8,754,131 ("the '131 patent"), and/or 8,871,813 ("the '813 patent"); all such information disclosed by Company to Recipients as described above is referred to as the "Confidential Information"; and

WHEREAS, as a condition to the Company furnishing the Confidential Information to Recipients, the Company requires that the Recipients agree to treat the Confidential Information as confidential in accordance with the terms of this Offer.

NOW, THEREFORE, Company offers to provide Recipients with Confidential Information, subject to the following terms and conditions:

1. Restrictions on Disclosure and Use of Confidential Information

(a) Confidential Information provided to the Recipients by the Company pursuant to this Offer will be used by Recipients solely for the purpose of evaluating the possible infringement of the '431, '290, '131 or '813 patents by Company's bromfenac sodium ophthalmic solution/drops EQ 0.07% acid product that is the subject of ANDA No. 207584 (the "Approved Use"). The Recipients are permitted to disclose the Confidential Information to: (i) Recipients' outside counsel (and their staff) with responsibilities related to this matter; (ii) two of Recipients' in house attorneys, provided that such in house attorneys are not directly responsible for research and development operations, filing citizen petitions, or patent prosecution efforts relating to propofol for injection products or methods of making or using propofol for injection products; and (iii) independent experts or consultants retained by Recipients' outside counsel ((i)-(iii) collectively, "Representatives"); provided, however, that prior to any such disclosure, the Recipients agree (i) to advise each Representative of the confidential nature of the Confidential Information, (ii) to direct each Representative to treat the Confidential Information as confidential, and (iii) that such Representative shall be bound by the provisions of this Offer to the same extent as the Recipients. Except as stated herein, neither the Recipients nor any of Recipients' Representatives shall disclose or divulge any of the Confidential Information to any other person or entity without the express prior written consent of the Company.

(b) The restrictions in the foregoing paragraph 1(a) shall not apply as to information that the Recipients can demonstrate by clear and convincing evidence through written records existing prior to the Effective Date of this Offer (i) that the Recipients or Recipients' Representatives already possessed such information without obligation of confidentiality, (ii) that the Recipients developed such information independently and without the Confidential Information, (iii) that the Recipients rightfully received such information from a third party without obligation of confidentiality, or (iv) that such information is or has become publicly available without violation of any of the terms of this Offer.

(c) Nothing in this Offer shall be construed to prevent the Recipients from making any disclosure of any Confidential Information if required to do so by any applicable law or regulation. If the Recipients or any of Recipients' Representatives are requested or required by applicable law or regulation (through interrogatories, requests for information or documents, subpoena, civil investigative demand or similar process) to disclose any of the information in the Confidential Information, the Recipients and/or Recipients' Representative agree to provide the Company with prompt notice of such request so that the Company may seek an appropriate protective order. Failure to provide prompt notice shall constitute a material breach of this Offer.

2. Rights and Remedies

(a) The Recipients agree to be responsible for any breach of any provision of this Offer by Recipients' Representatives. The Recipients agree, at Recipients' sole expense, to take all reasonable measures, including but not limited to initiating court proceedings, to restrain Recipients' Representatives from unauthorized disclosure or use of the Confidential Information. Nothing in this paragraph shall be construed to limit Company's rights to take direct action against Recipients' Representatives.

(b) The Recipients acknowledge and agree that monetary damages may not be a sufficient remedy for any material breach of this Offer by Recipients or by any of Recipients' Representatives and that the Company will be entitled to specific performance and/or injunctive relief as remedies for any such breach. The Recipients agree that no bond or other security shall be required in obtaining such equitable relief.

(c) The Recipients agree that they shall have access to the Confidential Information for up to 45 days from Recipients' receipt of the Confidential Information. At that time, or upon the request of the Company, Recipients shall promptly deliver to the Company, or at Recipients' option, certify that Recipients have destroyed, all originals, copies, reproductions and non-privileged summaries of the Confidential Information kept by Recipients and to certify to that effect, except that Recipients' outside law firm may keep one archival copy of the information on an "Attorneys Eyes Only" basis and may continue to provide advice to Recipients if necessary, consistent with the terms of this Offer. Notwithstanding the return of the Confidential Information, the Recipients and Recipients' representatives will continue to be bound by their obligations of confidentiality and other obligations under this Offer.

3. Miscellaneous

(a) The terms of this Offer may be modified or waived only by separate writing between Company and Recipients expressly so modifying or waiving such terms.

(b) The Recipients further understand, acknowledge and agree that no failure or delay by the Company in exercising any right, power or privilege hereunder shall operate as a waiver hereof; nor shall any single or partial exercise thereof preclude any other or further exercise of any right, power or privilege hereunder.

(c) This Offer shall be governed by and construed in accordance with the laws of Wisconsin, without reference to its choice of law principles.

(d) This Offer may not be assigned by Recipients by merger, operation of law, or otherwise except with the express prior written consent of the Company, and shall be binding upon the Recipients' heirs, successors, and permitted assignees.

(e) This Offer shall be considered withdrawn and of no effect if Recipients do not request access to the Confidential Information within 40 days of the Effective Date, by signing the request found on the signature page of this Offer.

[Signature Page Follows]

IN WITNESS WHEREOF, Company has provided this Offer as of the date first written above.

Paddock Laboratories, LLC

Print Name: Jeffrey S. Ward

By: 

Title: Attorney for Paddock Laboratories, LLC Date: December 15, 2014

IN WITNESS WHEREOF, Recipients hereby requests confidential access to information relating to ANDA No. 207584, and hereby agree to be bound by all terms and provisions contained in this Offer.

Bausch & Lomb Incorporated

Print Name: _____

By: _____

Title: _____ Date: _____

Senju Pharmaceutical Co., Ltd.

Print Name: _____

By: _____

Title: _____ Date: _____

From: (608) 280-6761
Julie King
Merchant 26 Gould
Merchant & Gould
10 East Doty Street Suite 600
Madison, WI 53703

Origin ID: LNRA

FedEx Express

J142214092303uv

Ship Date: 15DEC14
ActWgt: 0.5 LB
CAD: 105320530/INET3550

Delivery Address Bar Code

Ref # 16289.0047USVA
Invoice #
PO #
Dept #

SHIP TO: (866) 258-6245 BILL SENDER

J. Michael Pearson, CEO
Bausch & Lomb Inc.
1400 North Goodman Street

ROCHESTER, NY 14609

TUE - 16 DEC AA
STANDARD OVERNIGHT

TRK# 0201 7722 4261 4713

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