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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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13/687,242

11/28/2012

Shirou SAWA

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EXAMINER

SOROUGH, LAYLA

ART UNIT

PAPER NUMBER

1627

NOTIFICATION DATE

DELIVERY MODE

08/01/2013

ELECTRONIC

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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## Office Action Summary

Application No.  
13/687,242

Applicant(s)  
SAWA ET AL.

Examiner  
LAYLA SOROUGH

Art Unit  
1627

AIA (First Inventor to File)  
Status  
No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 9 April 2013.  
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on \_\_\_\_\_.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on \_\_\_\_\_; the restriction requirement and election have been incorporated into this action.
- 4) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 5) ☒ Claim(s) 29-48 is/are pending in the application.  
5a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 6) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 7) ☒ Claim(s) 29-48 is/are rejected.
- 8) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 9) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

\* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see [http://www.uspto.gov/patents/init\\_events/pph/index.jsp](http://www.uspto.gov/patents/init_events/pph/index.jsp) or send an inquiry to [PPHfeedback@uspto.gov](mailto:PPHfeedback@uspto.gov).

### Application Papers

- 10) ☐ The specification is objected to by the Examiner.
- 11) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

#### Certified copies:

- a) ☐ All b) ☐ Some \* c) ☐ None of the:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☒ Information Disclosure Statement(s) (PTO/SB/08)  
Paper No(s)/Mail Date 11/28/12
- 3) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_
- 4) ☐ Other: \_\_\_\_\_

### **DETAILED ACTION**

The Office Action is in response to the Applicant's reply filed April 9, 2013 to the restriction requirement made on March 25, 2013.

Applicant's election of benzalkonium chloride as the species of quarternary ammonium salts is hereby acknowledged. . Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 19-48 read on the elected species.

The requirement is still deemed proper and is therefore made **FINAL**.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of 35 U.S.C. 112(b):

(b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 44-48 rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA),

second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention. Applicant has claimed the preservative efficacy standard is satisfied by EP-criteria B of the European Pharmacopoeia. Where possible, claims are to be complete in themselves. Incorporation by reference to a specific figure or table "is permitted only in exceptional circumstances where there is no practical way to define the invention in words and where it is more concise to incorporate by reference than duplicating a drawing or table into the claim. Incorporation by reference is a

Art Unit: 1627

necessity doctrine, not for applicant's convenience." Ex parte Fressola, 27 USPQ2d 1608, 1609 (Bd. Pat. App. & Inter. 1993) (citations omitted).

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 19, 21-24, 26, 28-30, 32, 34-36, 38, 40-42, and 44-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gamache, et al. (WO 01/15677 A2; 03/2001).

Gamache teaches compositions for otic and intranasal use (p.6, lines 5-6) that contain a combination of a 5-HT agonist and an anti-inflammatory agent (p. 6, lines 1-4; p. 12 lines 9-10) or alternatively sequential or concurrent dosing of separate compositions that contain the 5-HT antagonist in one composition and the anti-inflammatory agent in a second composition (p. 12, lines 9-11); specifically claimed is the anti-inflammatory specie bromfenac (2-amino-3-(4-bromobenzoyl)phenylacetic acid). Typical concentrations of anti-inflammatory agents, such as bromfenac, are taught in the range 0.01-1.0 % (w/v) (overlapping with 0.01-0.5; p. 13, lines 6-8); aqueous formulations are preferred (p. 10, lines 11-14); tyloxapol is taught in a concentration of 0.05 % (w/v) (p. 16, line 30). The salt form of bromfenac in solution will be the same when the acid is dissolved in a solution followed by adjustment to the desired pH with NaOH/HCl (Gamache, p. 15, line 33) as when the sodium salt is dissolved in solution adjusted to the same pH; in this case Gamache also teaches the sodium salt limitation of instant claim 21. The concentration range of 0.01-1.0% overlaps and encompasses the claimed concentration range of the sodium salt of bromfenac instantly claimed.

Although, the reference does not exemplify an aqueous liquid preparation comprising the first component and second component, it would have been obvious

Art Unit: 1627

for one of ordinary skill in the art at the time of the invention to select concentrations of bromfenac in the invention of Gamache. It would have been obvious to adjust the concentration of tyloxapol, to see what the effect would be on the solubility and stability of the aqueous preparations, which would have resulted in the effective concentrations of the instant claims. It would also have been obvious to adjust the pH to values in the 7.5 to 8.5 range, with the potential of dissolving and/or stabilizing more of the acidic drug, bromfenac, in a more aqueous soluble ionic form. The motivation would have been to prepare pharmaceutical products with optimal drug dosage and stability. Hence, a skilled artisan would have reasonable expectation of successfully producing an efficacious and stable drug.

Claims 20, 27, 33, and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gamache, et al. (WO 01/15677 A2; 03/2001), as applied to claims 19, 21-24, 26, 28-30, 32, 34-36, 38, 40-42, and 44-48 and further in view of Desai, et al. (5558876).

Gamache, et al. is as discussed above.

Gamache, et al. fails to teach quaternary ammonium salt

Desai et al. teaches a composition comprising 0.05% Bromfenac, 0.05% Disodium EDTA, and 0.01% Benzalkonium chloride.

It would have been obvious to one of ordinary skill in the art to incorporate benzalkonium chloride into the ophthalmic formulation. The motivation comes from the teaching that benzalkonium chloride acts as a preservative in ophthalmic

Art Unit: 1627

formulation. Hence, a skilled artisan would have had reasonable expectation of successfully producing similar efficacy and results.

Claims 25, 31, 37, and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gamache, et al. (WO 01/15677 A2; 03/2001), as applied to claims 19, 21-24, 26, 28-30, 32, 34-36, 38, 40-42, and 44-48 and further in view of Ogawa, et al. (US 4910225 A) and De Bruij et al. (US 6162393 A).

Gamache, et al. is as discussed above.

Gamache, et al. fails to teach sodium tetraborate, sodium sulfite, and polyvinylpyrrolidone, boric acid.

Ogawa et al. teaches sodium sulfite and polyvinyl pyrrolidone increased the stability of an eye drop formulation remarkably. The pH adjustment is generally conducted with sodium hydroxide or hydrochloric acid, for instance, and it is advisable to form a buffer solution by combined use of, for example, sodium acetate, sodium borate or sodium phosphate and acetic acid, boric acid or phosphoric acid, respectively.

De Bruij et al. various buffer systems such as citrate, phosphate (appropriate mixtures of  $\text{Na}_2\text{HPO}_4$ ,  $\text{NaH}_2\text{PO}_4$ , and  $\text{KH}_2\text{PO}_4$ ), borate (boric acid, sodium tetraborate) potassium metaborate and mixtures), bicarbonate, and tromethamine and other appropriate nitrogen-containing buffers (such as ACES, BES, BICINE, BIS-Tris, BIS-Tris Propane, HEPES, HEPPS, imidazole, MES, MOPS, PIPES, TAPS, TES, Tricine) can be used to ensure a physiologic pH between about pH 6.5 and 8.5 in an eye solution.

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

### ***Double Patenting***

Claims 19, 21-24, 26, 28-30, 32, 34-36, 38, 40-42, and 44-48 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-8 of U.S. Patent No. 7829544. Although the claims at issue are not identical, they are not patentably distinct from each other because the claims in the patent are drawn to an aqueous solution preparation comprising (a) an aminoglycoside antibiotic or its pharmacologically acceptable salt, (b) bromfenac or its pharmacologically acceptable salt and (c) nicotinamide whereas the claims herein are drawn to a stable aqueous liquid preparation comprising: (a) a first component; and (b) a second component; wherein the first component is 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a



Art Unit: 1627

pharmacologically acceptable salt thereof or a hydrate thereof, wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate; the second component is tyloxapol and is present in said liquid preparation in an amount sufficient to stabilize said first component; and wherein said stable liquid preparation is formulated for ophthalmic administration.

Claims 19, 21-24, 26, 28-30, 32, 34-36, 38, 40-42, and 44-48 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-22 of U.S. Patent No. 8129431. Although the claims at issue are not identical, they are not patentably distinct from each other because the claims in the patent are drawn to an aqueous liquid preparation consisting essentially of the following two components, wherein the first component is 2-amino-3-(4-bromobenzoyl)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 whereas the claims herein are drawn to a stable aqueous liquid preparation comprising: (a) a first component; and (b) a second component; wherein the first component is 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate; the second component is tyloxapol and is present

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

Claims 19, 21-24, 26, 28-30, 32, 34-36, 38, 40-42, and 44-48 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-5 of copending Application No. 11755662. Although the claims at issue are not identical, they are not patentably distinct from each other because the claims in the copending application are drawn to a method of treating pain and/or inflammation associated with an ocular disease, injury or disorder comprising administering to a patient, in need of such treatment, a stabilized aqueous liquid solution comprising 2-amino-3-(4-bromobenzoyl) phenylacetic acid or a pharmaceutically acceptable salt thereof or a hydrate thereof at a concentration ranging from 0.05% to 0.1% administered once or twice a day, or at a concentration ranging from 0.12% to 0.24% administered once a day, and an alkyl aryl polyether alcohol type polymer whereas the claims herein are drawn to a stable aqueous liquid preparation comprising: (a) a first component; and (b) a second component; wherein the first component is 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate; the second component is tyloxapol and is present in said liquid preparation in an amount sufficient to stabilize said first component; and wherein said stable liquid preparation is formulated for ophthalmic administration.

This is a provisional nonstatutory double patenting rejection.

Claims 19, 21-24, 26, 28-30, 32, 34-36, 38, 40-42, and 44-48 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-5 of copending Application No. 13353653. Although the claims at issue are not identical, they are not patentably distinct from each other because the claims in the copending application are drawn to an aqueous liquid preparation comprising 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt thereof or a hydrate thereof, and polyoxyl 40 stearate, wherein the concentration of the polyoxyl 40 stearate is selected from a range of a minimum concentration of 0.02 w/v % to a maximum concentration of 0.1 w/v% whereas the claims herein are drawn to a stable aqueous liquid preparation comprising: (a) a first component; and (b) a second component; wherein the first component is 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate; the second component is tyloxapol and is present in said liquid preparation in an amount sufficient to stabilize said first component; and wherein said stable liquid preparation is formulated for ophthalmic administration.

This is a provisional nonstatutory double patenting rejection.

## Conclusion

No claims allowed.

Art Unit: 1627

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Layla Soroush whose telephone number is (571)272-5008. The examiner can normally be reached on Monday through Friday from 8:30 a.m. to 5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Layla Soroush/

Examiner, Art Unit 1627