[redacted]

FILED UNDER 35 U.S.C. 371

U.S. UTILITY Patent Application

PATENT NUMBER and ISSUE DATE
8,388,941

APPLICATION NUMBER	FILING DATE	CLASS	SUBCLASS	GROUP ART UNIT	EXAMINER
12/441,995					

(FACE)

BEST AVAILABLE COPY

NOTICE OF ALLOWANCE MAILED		Assistant Examiner	CLAIMS ALLOWED	
			Total Claims	Print Claim for O.G
ISSUE FEE			DRAWING	
Amount Due	Date Paid		Sheets Drwg. / Figs.Drwg. / Print Fig.	
☐ TERMINAL DISCLAIMER		Primary Examiner	Application Examiner	
		PREPARED FOR ISSUE		

WARNING: The information disclosed herein may be restricted. Unauthorized disclosure may be prohibited by the United States Code Title 35, Sections 122, 181 and 368, Possession outside the U.S. Patent & Trademark Office is restricted to authorized employees and contractors only.

FILED WITH: ☐ DISK (CRF) ☐ CD-ROM
(Attached in pocket on right inside flap)

PTO-1390 (Rev. 09-08)
Approved for use through 2/28/2010. OMB 0651-0021
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A SUBMISSION UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	
2667 US F	
U.S. APPLICATION NO. (If known, see 37 CFR 1.5)	

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/US2007/079094	September 20, 2007	September 28, 2006

TITLE OF INVENTION
SELF-PRESERVED AQUEOUS PHARMACEUTICAL COMPOSITIONS

APPLICANT(S) FOR DO/EO/US
ALCON RESEARCH, LTD.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☑ This is a **FIRST** submission of items concerning a submission under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a submission under 35 U.S.C. 371.
3. ☐ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below.
4. ☐ The US has been elected (Article 31).
5. ☑ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☐ is attached hereto (required only if not communicated by the International Bureau).
   b. ☐ has been communicated by the International Bureau.
   c. ☑ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. ☐ is attached hereto.
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☑ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   b. ☐ have been communicated by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☑ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☑ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ An English language translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11 to 20 below concern document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☑ A preliminary amendment.
14. ☐ An Application Data Sheet under 37 CFR 1.76.
15. ☐ A substitute specification.
16. ☐ A power of attorney and/or change of address letter.
17. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13*ter*.3 and 37 CFR 1.821- 1.825.
18. ☐ A second copy of the published International Application under 35 U.S.C. 154(d)(4).
19. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).

PTO-1390 (Rev. 09-08)
Approved for use through 2/28/2010. OMB 0651-0021
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

U.S. APPLICATION NO. (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
	PCT/US2007/079094	2667 US F

20. Other items or information:

The following fees have been submitted	CALCULATIONS	PTO USE ONLY
21. ☑ Basic national fee (37 CFR 1.492(a)) **$330**	$ 330.	
22. ☑ Examination fee (37 CFR 1.492(c)) If the written opinion prepared by ISA/US or the international preliminary examination report prepared by IPEA/US indicates all claims satisfy provisions of PCT Article 33(1)-(4) ..... **$0** All other situations **$220**	$ 220.	
23. ☑ Search fee (37 CFR 1.492(b)) If the written opinion of the ISA/US or the International preliminary examination report prepared by IPEA/US indicates all claims satisfy provisions of PCT Article 33(1)-(4) ..... **$0** Search fee (37 CFR 1.445(a)(2)) has been paid on the international application to the USPTO as an International Searching Authority ..... **$100** International Search Report prepared by an ISA other than the US and provided to the Office or previously communicated to the US by the IB ..... **$430** All other situations **$540**	$ 430.	
TOTAL OF 21, 22 and 23 =	$ 980.	

☐ Additional fee for specification and drawings filed in paper over 100 sheets (excluding sequence listing in compliance with 37 CFR 1.821(c) or (e) in an electronic medium or computer program listing in an electronic medium) (37 CFR 1.492(j)).
The fee is **$270** for each additional 50 sheets of paper or fraction thereof.

Total Sheets	Extra Sheets	Number of each additional 50 or fraction thereof (round **up** to a whole number)	RATE	
- 100 =	/50 =		x $270	$

Surcharge of **$130.00** for furnishing any of the search fee, examination fee, or the oath or declaration after the date of commencement of the national stage (37 CFR 1.492(h)).	$	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	- 20 =		x $ 52	$	
Independent claims	- 3 =		x $220	$	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ $390	$	
			TOTAL OF ABOVE CALCULATIONS =	$	
☐ Applicant claims small entity status. See 37 CFR 1.27. Fees above are reduced by ½.					
			SUBTOTAL =	$	
Processing fee of **$130.00** for furnishing the English translation later than 30 months from the earliest claimed priority date (37 CFR 1.492(i)). +				$	
			TOTAL NATIONAL FEE =	$ 980.	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$	
			TOTAL FEES ENCLOSED =	$	
			Amount to be refunded:	$	
			Amount to be charged	$ 980.	

PTO-1390 (Rev. 09-08)
Approved for use through 2/28/2010. OMB 0651-0021
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

a. ☐ A check in the amount of $ _____ to cover the above fees is enclosed.

b. ☑ Please charge my Deposit Account No. 010682 in the amount of $ 980. to cover the above fees.

c. ☑ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 010682.

d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038. The PTO-2038 should only be mailed or faxed to the USPTO. However, when paying the basic national fee, the PTO-2038 may NOT be faxed to the USPTO.

ADVISORY: If filing by EFS-Web, do **NOT** attach the PTO-2038 form as a PDF along with your EFS-Web submission. Please be advised that this is **not** recommended and by doing so your **credit card information may be displayed via PAIR**. To protect your information, it is recommended paying fees online by using the electronic payment method.

NOTE: Where an appropriate time limit under 37 CFR 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the International Application to pending status.

SEND ALL CORRESPONDENCE TO:

Alcon Research, Ltd.
Scott A. Chapple, IP Legal
6201 South Freeway
Mail Code TB4-8
Fort Worth, TX 76134-2099

SIGNATURE

Scott A. Chapple

NAME

46,287

REGISTRATION NUMBER

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Alcon Research, Ltd. et al.

Serial No.: NYA

Filed: March 19, 2009

Examiner: NYA

Group Art Unit: NYA

For: SELF-PRESERVED AQUEOUS PHARMACEUTICAL COMPOSITIONS

PRELIMINARY AMENDMENT

Mail Stop PCT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Please amend the application as follows:

IN THE SPECIFICATION:

Please add the following sentence below the title:

This application claims priority as a 371 application from PCT/US2007/079094 filed on September 20, 2007, and claims priority from United States Serial No. 60/827,417, filed on September 28, 2006.

Respectfully submitted,

ALCON RESEARCH, LTD.

March 19, 2009
Date

Scott A. Chapple, Agent
Reg. No. 46,287

Address for Correspondence:
Scott A. Chapple
Alcon Research, Ltd.
6201 S. Freeway, Mail Code TB4-8
Fort Worth, TX 76134-2099
Phone: 817-615-5288
Attorney Docket: 2667 US F

DECLARATION AND POWER OF ATTORNEY

As a below named inventor, we hereby declare that:

Our residence, post office address and citizenship are as stated below next to our names.

We believe we are the original, first and joint inventors of the subject matter which is claimed and for which a patent is sought on the invention entitled:

SELF PRESERVED AQUEOUS PHARMACEUTICAL COMPOSITIONS

described and claimed herewith and further identified as Attorney Docket No. 2667 US F the specification of which (check one)

(X) is attached hereto.

( ) was filed by an authorized person on my behalf on _____, as Application Serial No. _____ and was amended on _____ (if applicable)

We hereby state that we have reviewed and understand the contents of the above-identified specification, including the claims as amended by any amendment referred to above.

We acknowledge the duty to disclose information which is known to me to be material to patentability as defined in Section 1.56.

We hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT international application which designated at least one country other than the United States, listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s):			**Priority Claimed**	
Application Number	**Country**	**Filed (Month/Day/Year)**	**Yes**	**No**
PCT/US2007/079094	**US**	**09/20/2007**	**X**	

We hereby claim the benefit under 35 USC §119(e) of any United States provisional application(s) listed below.

Prior Provisional Application(s):		Priority Claimed	
Application Number	**Filed (Month/Day/Year)**	**Yes**	**No**
60/827,417	**09/28/2006**	**X**	

We hereby claim the benefit under Title 35, United States Code, Section 120 of any United States application(s), or Section 365(c) of any PCT international application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT international application in the manner provided by the first paragraph of Title 35, United States Code, Section 112. I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, Section 1.56 which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

Prior U.S. Application(s):		Status: Patent, Pending, Abandoned
Application Number	**Filed (Month/Day/Year)**	

We hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

We hereby appoint those patent practitioners associated with Customer No. **26356** as my attorneys, with full power of substitution and revocation, to prosecute this application and to transact all business in the United States Patent and Trademark Office connected therewith.

Full name of Inventor: Masood A. Chowhan

Address: 3521 Lake Tahoe Drive
Arlington, TX 76016

Inventor's Signature: Masood A. Chowhan

Date: 3/12/09

Citizenship: United States

Full name of Inventor: David J. Keith

Address: 508 Mill Creek Lane
Washington, MO 63090

Inventor's Signature: David J. Keith

Date: 3/9/09

Citizenship: United States

Address for Correspondence:
Alcon Research, Ltd.
Scott A. Chapple, IP Legal
6201 South Freeway, TB4-8
Fort Worth, TX 76134-2099
Phone: 817-615-5288
Docket No.: 2667 US F

Customer No.: 26356

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 2677FWO	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/US2007/079094	International filing date *(day/month/year)* 20.09.2007	Priority date *(day/month/year)* 28.09.2006
International Patent Classification (IPC) or national classification and IPC INV. A61K9/00		
Applicant Alcon Research, Ltd.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 4 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

- ☒ Box No. I Basis of the report
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
2008-07-25	11.12.2008
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Kardas-Llorens, Eyüp Telephone No. +49 89 2399-8652

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US2007/079094

Box No. I Basis of the report

1. With regard to the **language**, this report is based on

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3(a) and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4(a))
   - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-28 as originally filed

   Claims, Numbers

   1-10 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

5. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 70.2 (e)).

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-10
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-10
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-10
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Novelty:

A composition comprising a borate/polyol complex and zinc ions in the specified amounts as claimed in claim 1 is not disclosed in any one document cited in the search report.

The subject-matter of independent claims 1 and 6 is therefore new (Article 33(2) PCT).

Inventive Step:

The present problem to be solved by the present invention is to provide an ophthalmic composition with the desired antimicrobial activity to satisfy the preservation efficacy requirements.

This has been presently achieved by a composition comprising a borate/polyol complex and zinc ions as claimed which demonstrates the desired effects as demonstrated in present examples 4-6 in the claimed amounts of the actives.

From none of the cited prior art documents it was obvious to a person skilled in the art to combine a borate/polyol complex with a zinc compound to achieve the desired technical effects in the presently claimed concentrations.

The relevant prior art documents D1 (US2002/0123482), D2 (US2005/129771) and D3 (WO95/13050) comprise zinc below (D1 and D2) and above (D3) the minimum amount required in the ophthalmic composition which do not lead to the desired effects.

Thus, the solution to the problem proposed in claim 1 and 6 of the present application is considered as involving an inventive step (Article 33(3) PCT).

Re Item VIII

Certain observations on the international application

The wordings "having sufficient antimicrobial activity to satisfy USP preservative efficacy requirements" in claim 3 and 8 are not clear, since it is not clear how the "sufficient antimicrobial activity" and said "preservative efficacy requirements" have to be.

Also from the wording "conventional antimicrobial preservative" in claims 4 and 9 it is not clear which preservatives are meant.

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

To:
ALCON RESEARCH, LTD.
Attn. Brown, Gregg C.
6201 South Freeway
TB 4-8
Fort Worth TX 76134-2099
ETATS-UNIS D'AMERIQUE

Applicant's or agent's file reference ~~2677F~~WO	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/US2007/079094	International filing date *(day/month/year)* 20/09/2007
Applicant ALCON MANUFACTURING, LTD.	
	Date of mailing *(day/month/year)* 02/04/2008

1. [x] The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the International Search Report.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Fascimile No.: (41-22) 338.82.70

   For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   [ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

   [ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

   See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Georg Hutterer 4/15/08

Form PCT/ISA/220 (October 2005)

(See notes on accompanying sheet)

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report and the written opinion of the International Searching Authority, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims,description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only (see *PCT Applicant's Guide*, Volume I/A, Annexes B1 and B2).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, Volume I/A, paragraph 296).

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
2677FWO		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US2007/079094	20/09/2007	28/09/2006
Applicant		
ALCON MANUFACTURING, LTD.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language,** the international search was carried out on the basis of:
      [X] the international application in the language in which it was filed
      [ ] a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. [ ] This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [ ] **Certain claims were found unsearchable** (See Box No. II)

3. [ ] **Unity of invention is lacking** (see Box No III)

4. With regard to the **title,**
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings,**
   a. the figure of the **drawings** to be published with the abstract is Figure No. _____
      [ ] as suggested by the applicant
      [ ] as selected by this Authority, because the applicant failed to suggest a figure
      [ ] as selected by this Authority, because this figure better characterizes the invention
   b. [ ] none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/079094

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/00 A61K31/00 A61K47/02 A61K47/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2002/123482 A1 (CHOWHAN MASOOD A [US] ET AL) 5 September 2002 (2002-09-05) paragraphs [0013], [0016], [0019], [0021] - [0024]; claims 1,15,16	1-10
X	US 2005/129771 A1 (ASGHARIAN BAHRAM [US]) 16 June 2005 (2005-06-16) paragraphs [0016] - [0019], [0024], [0027], [0030], [0032]; example 2	1-10
X	WO 95/13050 A (CIBA GEIGY AG [CH]; OLEJNIK OREST [US]; WENDEL FRED W [US]) 18 May 1995 (1995-05-18) page 2, line 8 - page 4, line 5; claims 1-25	1-10

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 March 2008	02/04/2008

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Rauter, Anton

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Form PCT/ISA/210 (second sheet) (April 2005)

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 6 143 799 A (CHOWHAN MASOOD [US] ET AL) 7 November 2000 (2000-11-07) claims 1-21	1-10
Y	WO 2005/097067 A (BAUSCH & LOMB [US]; XIA ERNING [US]; SALAMONE JOSEPH C [US]; BORAZJANI) 20 October 2005 (2005-10-20) claims 1-78	1-10

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2007/079094

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2002123482 A1	05-09-2002	NONE	
US 2005129771 A1	16-06-2005	NONE	
WO 9513050 A	18-05-1995	AU 8060394 A	29-05-1995
		CA 2173255 A1	18-05-1995
		US 5597559 A	28-01-1997
		ZA 9408961 A	13-07-1995
US 6143799 A	07-11-2000	NONE	
WO 2005097067 A	20-10-2005	AU 2005231147 A1	20-10-2005
		BR PI0509363 A	11-09-2007
		CA 2560724 A1	20-10-2005
		CN 1938003 A	28-03-2007
		EP 1734923 A1	27-12-2006
		JP 2007530685 T	01-11-2007
		KR 20060135006 A	28-12-2006
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(71) Applicant *(for all designated States except US)*: **ALCON MANUFACTURING, LTD.** [US/US]; 6201 South Freeway, Mail Code TB4-8, Fort Worth, Texas 76134-2099 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **CHOWHAN, Masood A.** [US/US]; 3521 Lake Tahoe Dr., Arlington, Texas 76016 (US). **KEITH, David, J.** [US/US]; 508 Millcreek Lane, Washington, Missouri 63090 (US).

(74) Agents: **BROWN, Gregg C.** et al.; 6201 South Freeway, Mail Code TB4-8, Fort Worth, Texas 76134-2099 (US).

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(54) Title: SELF-PRESERVED AQUEOUS PHARMACEUTICAL COMPOSITIONS

(57) Abstract: The use of a borate/polyol and zinc system to enhance the antimicrobial activity of multi-dose pharmaceutical compositions is described. The compositions do not require a conventional anti-microbial preservative and therefore are referred to as being 'self-preserved'. The compositions possess sufficient antimicrobial activity to satisfy the preservative efficacy requirements of the USP for aqueous ophthalmic compositions.

SELF-PRESERVED AQUEOUS PHARMACEUTICAL COMPOSITIONS

Background of the Invention

The present invention is directed to self-preserved pharmaceutical compositions. More specifically, the invention is directed to the provision of aqueous, multi-dose pharmaceutical compositions that have been formulated so as to have sufficient antimicrobial activity to satisfy the preservation efficacy requirements of the United States Pharmacopeia ("USP") and analogous guidelines in other countries, without requiring a conventional antimicrobial preservative, such as benzalkonium chloride, polyquaternium-1, hydrogen peroxide (e.g., sodium perborate), or chorine-containing agents. The ability to achieve self-preservation is based on a unique combination of formulation components and criteria.

Many pharmaceutical compositions are required to be sterile (i.e., free of bacteria, fungi and other pathogenic microorganisms). Examples of such compositions include: solutions and suspensions that are injected into the bodies of humans or other mammals; creams, lotions, solutions or other preparations that are topically applied to wounds, abrasions, burns, rashes, surgical incisions, or other conditions where the skin is not intact; and various types of compositions that are applied either directly to the eye (e.g., artificial tears, irrigating solutions, and drug products), or are applied to devices that will come into contact with the eye (e.g., contact lenses).

The foregoing types of compositions can be manufactured under sterile conditions via procedures that are well known to those skilled in the art. However, once the packaging for a product is opened, such that the composition contained therein is exposed to the atmosphere and other sources of potential microbial contamination (e.g., the hands of a human patient), the sterility of the product may be

compromised. Such products are typically utilized multiple times by the patient, and are therefore frequently referred to as being of a "multi-dose" nature.

Due to the frequent, repeated exposure of multi-dose products to the risk of microbial contamination, it is necessary to employ a means for preventing such contamination from occurring. The means employed may be: (i) a chemical agent that prevents the proliferation of microbes in a composition, which is referred to herein as an "antimicrobial preservative"; or (ii) a packaging system that prevents or reduces the risk of microbes reaching a pharmaceutical composition within a container.

Prior multi-dose ophthalmic compositions have generally contained one or more antimicrobial preservations in order to prevent the proliferation of bacteria, fungi and other microbes. Such compositions may come into contact with the cornea either directly or indirectly. The cornea is particularly sensitive to exogenous chemical agents. Consequently, in order to minimize the potential for harmful effects on the cornea, it is preferable to use anti-microbial preservatives that are relatively non-toxic to the cornea, and to use such preservatives at the lowest possible concentrations (i.e., the minimum amounts required in order to perform their anti-microbial functions).

Balancing the anti-microbial efficacy and potential toxicological effects of anti-microbial preservatives is sometimes difficult to achieve. More specifically, the concentration of an antimicrobial agent necessary for the preservation of ophthalmic formulations from microbial contamination may create the potential for toxicological effects on the cornea and/or other ophthalmic tissues. Using lower concentrations of the anti-microbial agents generally helps to reduce the potential for such toxicological effects, but the lower concentrations may be insufficient to achieve the required level of biocidal efficacy (i.e., antimicrobial preservation).

The use of an inadequate level of antimicrobial preservation may create the potential for microbial contamination of the compositions and ophthalmic infections resulting from such contaminations. This is also a serious problem, since ophthalmic infections involving *Pseudomonas aeruginosa* or other virulent microorganisms can lead to loss of visual function or even loss of the eye.

Thus, there is a need for a means of enhancing the activity of anti-microbial agents so that very low concentrations of the agents can be utilized without increasing the potential for toxicological effects or subjecting patients to unacceptable risks of microbial contamination and resulting ophthalmic infections.

Ophthalmic compositions are generally formulated as isotonic, buffered solutions. One approach to enhancing the anti-microbial activity of such compositions is to include multi-functional components in the compositions. In addition to performing their primary functions, these multi-functional components also serve to enhance the overall anti-microbial activity of the compositions.

The following publications may be referred to for further background regarding the use of multi-functional components to enhance the antimicrobial activity of ophthalmic compositions:

1. U.S. Patent No. 5,817,277 (Mowrey-McKee, et al; tromethamine);
2. U.S. Patent No. 6,503,497 (Chowhan, et al.; borate/polyol complexes);
3. U.S. Patent No. 5,741,817 (Chowhan, et al.; low molecular weight amino acids such as glycine);
4. U.S. Patent No. 6,319,464 (Asgharian; low molecular weight amino alcohols); and
5. U.S. Patent Application Publication No. US 2002/0122831 A1 (Mowrey-McKee, et al.; bis-aminopolyols).

The present invention is also based in-part on a finding that zinc further enhances the antimicrobial activity of ophthalmic compositions containing borate/polyol complexes of the type described herein. The use of zinc to enhance the antimicrobial activity of pharmaceutical compositions, including ophthalmic solutions, is well known. See, for example, the following articles and patent publications, as well as U.S. Patent No. 6,348,190 and JP 2003-104870, cited above:

McCarthy, "Metal Ions and Microbial Inhibitors", Cosmetic & Toiletries, 100:69-72 (Feb. 1985);

Zeelie, et al., "The Effects of Selected Metal Salts on the Microbial Activities of Agents used in the Pharmaceutical and Related Industries", Metal Compounds in Environment and Life, 4:193-200 (1992);

Zeelie, et al., "Effects of Copper and Zinc Ions on the Germicidal Properties of Two Popular Pharmaceutical Antiseptic Agents, Cetylpyridinium Chloride and Povidone-iodine", Analyst, 123:503-507 (March 1998);

McCarthy, et al., "The Effect of Zinc Ions on the Antimicrobial Activity of Selected Preservatives", Journal of Pharmacy and Pharmacology, Vol. 41 (1989);

U.S. Patent No. 6,482,799 (Tuśe, et al.);

U.S. Patent No. 5,320,843 (Raheja, et al.);

U.S. Patent No. 5,221,664 (Berkowitz, et al.);

U.S. Patent No. 6,034,043 (Fujiwara, et al.);

U.S. Patent No. 4,522,806 (Muhlemann, et al.);

U.S. Patent No. 6,017,861 (Fujiwara, et al.); and

U.S. Patent No. 6,121,315 (Nair, et al.).

However, the use of zinc ions in combination with borate/polyol complexes, as described herein is not disclosed or suggested by the prior art.

The compositions of the present invention are multi-dose products that do not contain a conventional antimicrobial preservative (e.g., benzalkonium chloride), but yet are preserved from microbial contamination. Such compositions have been referred to in the art as being "preservative free" (see, e.g., U.S. Patent No. 5,597,559 issued to Olejnik, et al.). Compositions that are preserved from microbial contamination as a result of the inherent antimicrobial activity of one or more components of the compositions are also referred to in the art as being "self-preserved" (see, e.g., U.S. Patent No. 6,492,361 issued to Muller, et al.).

The following publication may be referred to for further background regarding pharmaceutical compositions that are "preservative-free" or "self-preserving": Kabara, et al., Preservative-Free and Self-Preserving Cosmetics and Drugs – Principles and Practice, Chapter 1, pages 1-14, Marcel Dekker, Inc. (1997).

The multi-dose compositions of the present invention, which do not contain a conventional antimicrobial preservative are referred to herein as being "self-preserved".

Summary of the Invention

The present invention is based on a finding that zinc is capable of enhancing the antimicrobial activity of aqueous pharmaceutical compositions containing

borate/polyol complexes, when utilized as described herein, so as to create aqueous, multi-dose compositions that satisfy the preservative efficacy requirements of the USP without a conventional antimicrobial preservative.

The self-preserved, multi-dose compositions of the present invention have several advantages over existing ophthalmic formulations that are either: (i) packaged as a "single dose" or "unit of use" product, so as to avoid the inclusion of any antimicrobial preservative (e.g., BION®TEARS Lubricant Eye Drops, which is marketed by Alcon Laboratories, Inc.), or (ii) preserved by means of a so-called "disappearing" preservatives, such as the chlorite-based system described in U.S. Patent Nos. 5,424,078; 5,736,165; 6,024,954; and 5,858,346 (e.g., the artificial tears product "REFRESH™ Tears", which is marketed by Allergan), or the peroxide-containing system described in U.S. Patent Nos. 5,607,698; 5,683,993; 5,725,887; and 5,858,996 (e.g., the artificial tear product "GenTeal™ Tears", which is marketed by CIBAVision).

Unlike these existing products, the multi-dose ophthalmic compositions of the present invention are able to satisfy the USP preservative efficacy requirements without employing any conventional antimicrobial preservatives, such as chlorite or hydrogen peroxide.

The above-discussed findings regarding the zinc may be applied to enhance the antimicrobial activity of various types of pharmaceutical compositions. However, the present invention is particularly directed to the provision of aqueous ophthalmic solutions that are effective in preventing microbial contamination in the absence of conventional antimicrobial preservatives, such as benzalkonium chloride ("BAC"), polyquaternium-1, chlorite or hydrogen peroxide.

Detailed Description of the Invention

The pharmaceutical compositions of the present invention contain a borate/polyol complex and zinc ions in amounts sufficient to enhance the antimicrobial activity of the compositions, such that a conventional antimicrobial preservative is not required.

As used herein, the term "borate" includes boric acid, salts of boric acid, other pharmaceutically acceptable borates, and combinations thereof. The following borates are particularly preferred: boric acid, sodium borate, potassium borate and combinations thereof. The use of borates containing divalent cations (e.g., calcium borate) may adversely affect the antimicrobial action of zinc ions, by competing with zinc for binding sites on the cell walls of bacterial and other microbes, and is therefore not preferred. For the same reason, the self-preserved compositions of the present invention are preferably free of or substantially free of other sources of divalent cations, such as calcium chloride.

As used herein, the term "polyol" includes any compound having at least one hydroxyl group on each of two adjacent carbon atoms that are not in *trans* configuration relative to each other. The polyols can be linear or cyclic, substituted or unsubstituted, or mixtures thereof, so long as the resultant complex is water soluble and pharmaceutically acceptable. Examples of such compounds include: sugars, sugar alcohols, sugar acids and uronic acids. Preferred polyols are sugars, sugar alcohols and sugar acids, including, but not limited to: mannitol, glycerin, xylitol, sorbitol and propylene glycol. The use of sorbitol, propylene glycol, or a combination thereof is particularly preferred.

The self-preserved compositions of the present invention preferably contain one or more borates in an amount of from about 0.1 to about 2.0% w/v, more preferably 0.3 to 1.5% w/v, and most preferably 0.5 to 1.2% w/v. The compositions of the present invention preferably contain one or more polyols in an amount of from about 0.01 to about 5.0% w/v, more preferably 0.6 to 2.0% w/v.

The use of borate-polyol complexes to enhance antimicrobial activity is described in U.S. Patent No. 6,503,497 (Chowhan, et al.), the entire contents of which are hereby incorporated in the present specification by reference. The above-described borate/polyol complexes are utilized in the compositions of the present invention in an amount effective to enhance the antimicrobial activity of the composition. The total concentration of the borate/polyol complex will typically be in the range of 0.5 to 6.0 percent by weight ("wt.%").

The zinc may be provided in various forms, such as zinc chloride, zinc sulfate, zinc acetate or zinc carbonate. The use of zinc chloride is preferred. The amount of zinc chloride required to achieve this effect may vary somewhat from formulation to formulation, depending on the particular borate/polyol complex selected, but will generally be from about 0.0005% to about 0.005% w/v, preferably 0.00075 to 0.0025% w/v.

In general, the self-preserved compositions of the present invention will preferably contain zinc, either in the form of zinc chloride or other zinc salts, at a molar concentration of 0.000017 moles/liter to 0.00017 moles/liter, preferably 0.000026 moles/liter to 0.00009 moles/liter. However, the concentration of zinc may be as high as 0.0035 moles/liter.

The manner in which zinc enhances antimicrobial activity in the compositions of the present invention is not completely understood. However, it is believed that zinc atoms enhance the antimicrobial activity of borates by forming bridges between the borate groups

The present invention is particularly directed to the provision of multi-dose, self-preserved ophthalmic compositions that contain zinc and borate in amounts sufficient to allow the compositions to satisfy the USP preservative efficacy requirements, as well as other preservative efficacy standards for aqueous pharmaceutical compositions, without a conventional antimicrobial preservative.

Relative to bacteria, the USP 27 Antimicrobial Effectiveness Test requires that multi-dose ophthalmic compositions have sufficient antimicrobial activity to reduce an initial inoculum of approximately 10^5 to 10^6 bacteria by one log (i.e., a 90% reduction in the microorganism population) over a period of seven (7) days and by three logs (i.e., a 99.9% reduction in the microorganism population) over a period of fourteen (14) days, and requires that there cannot be any increase in the microorganism population following the conclusion of the fourteen day period. Relative to fungi, the USP standards require that the compositions maintain stasis (i.e., no growth) relative to the population of the initial inoculum over the entire 28 day test period. The margin of error in calculating microorganism populations is generally accepted to be 0.5 logs. Accordingly, the term "stasis" as utilized relative to the above-discussed USP standards means that the initial fungi population cannot increase by more than 0.5 log orders, relative to the initial population.

The preservative efficacy standards for multi-dose ophthalmic solutions in the U.S. and other countries/regions are set forth in the following table:

Preservative Efficacy Test ("PET") Criteria

(Log Order Reduction of Microbial Inoculum Over Time

	Bacteria	Fungi
USP 27	A reduction of 1 log (90%), by day 7; 3 logs (99.9%) by day 14; and no increase after day 14	The compositions must demonstrate over the entire test period, which means no increases of 0.5 logs or greater, relative to the initial inoculum.
Japan	3 logs by 14 days; and no increase from day 14 through day 28.	No increase from initial count at 14 and 28 days
Ph. Eur. A[1]	A reduction of 2 logs (99%) by 6 hours; 3 logs by 24 hours; and no recovery after 28 days	A reduction of 2 logs (99%) by 7 days, and no increase thereafter
Ph. Eur. B	A reduction of 1 log at 24 hours; 3 logs by day 7; and no increase thereafter	A reduction of 1 log (90%) by day 14, and no increase thereafter
FDA/ISO 14730	A reduction of 3 logs from initial challenge at day 14; and a reduction of 3 logs from rechallenge	No increase higher than the initial value at day 14, and no increase higher than the day 14 rechallenge count through day 28.

[1]There are two preservative efficacy standards in the European Pharmacopoeia ' "A" and "B".

The standards identified above for the USP 27 are substantially identical to the requirements set forth in prior editions of the USP, particularly USP 24, USP 25 and USP 26.

The compositions of the present invention may also include one or more low molecular weight amino alcohols. The amino alcohols which may be utilized in the present invention are water-soluble and have a molecular weight in the range of from about 60 to about 200. The following compounds are representative of the low molecular weight amino alcohols which may be utilized in the present invention: 2-amino-2-methyl-1-propanol (AMP), 2-dimethylamino-methyl-1-propanol (DMAMP),

2-amino-2-ethyl-1,3-propanediol (AEPD), 2-amino-2-methyl-1,3-propanediol (AMPD), 2-amino-1-butanol (AB). "AMP (95%)", which refers to 95% pure AMP and 5% water, is the most preferred low molecular weight amino alcohol of the present invention. These amino alcohols are available commercially from Angus Chemical Company (Buffalo Grove, Illinois).

The amount of amino alcohol used will depend on the molecular weight of the amino alcohol selected, and the presence (or absence) of other ingredients in the composition (e.g., chelating agents, buffering agents and/or tonicity agents). The amino alcohol will generally be present in an amount necessary to enhance the antimicrobial activity of an aqueous self-preserved pharmaceutical composition of the type described herein. The amount of amino alcohol required for a particular composition can be determined through comparative testing, such as the tests described in Example 6 hereof. The above-described amino alcohols are also utilized in the compositions of the present invention to neutralize the pH of the borate or borate/polyol complex, or bring the composition to the desired pH level. The amount of amino alcohol required for this purpose is a function of the particular borate or borate/polyol mixture selected and the concentration thereof. In general, the self-preserved compositions of the present invention will contain one or more amino alcohols at a total concentration of from about 0.01 to about 2.0 percent by weight/volume ("%w/v"), and preferably from 0.1 to 1.0 %w/v.

The zinc and borate/polyol preservative systems described herein may be included in various types of pharmaceutical compositions to enhance anti-microbial activity and self-preserve the compositions, such as ophthalmic, otic, nasal and dermatological compositions, but is particularly useful in ophthalmic compositions. Examples of such compositions include: ophthalmic pharmaceutical compositions, such as topical compositions used in the treatment of glaucoma, infections, allergies or inflammation; compositions for treating contact lenses, such as cleaning products and products for enhancing the ocular comfort of patients wearing contact lenses; and

various other types of ophthalmic compositions, such as ocular lubricating products, artificial tears, astringents, and so on. The compositions may be aqueous or non-aqueous, but will generally be aqueous.

The ophthalmic pharmaceutical compositions of the present invention may contain various types of therapeutic agents. Examples of possible therapeutic agents include beta-blockers (e.g., timolol, betaxolol, levobetaxolol, carteolol, levobunolol, and propranolol), carbonic anhydrase inhibitors (e.g., brinzolamide and dorzolamide), alpha-1 antagonists (e.g., nipradolol), alpha-2 agonists (e.g. iopidine and brimonidine), miotics (e.g., pilocarpine and epinephrine), prostaglandin analogs (e.g., latanoprost, travoprost and unoprostone), hypotensive lipids (e.g., bimatoprost and compounds set forth in U.S. Pat. No. 5,352,708), neuroprotectants (e.g., memantine), serotonergics [e.g., 5-HT_2 agonists, such as S-(+)-1-(2-aminopropyl)-indazole-6-ol)], anti-angiogenesis agents (e.g., anecortave acetate), anti-infective agents (e.g., quinolones, such as moxifloxacin and gatifloxacin, and aminoglycosides, such as tobramycin and gentamicin), non-steroidal and steroidal anti-inflammatory agents (e.g., prednisolone, dexamethasone, lotoprednol, suprofen, diclofenac and ketorolac), growth factors (e.g., EGF), immunosuppressant agents (e.g., cyclosporin), and anti-allergic agents (e.g., olopatadine). The ophthalmic drug may be present in the form of a pharmaceutically acceptable salt, such as timolol maleate, brimonidine tartrate or sodium diclofenac. The compositions of the present invention may also include combinations of ophthalmic drugs, such as combinations of (i) a beta-blocker selected from the group consisting of betaxolol and timolol, and (ii) a prostaglandin analog selected from the group consisting of latanoprost, 1, 5-keto latanoprost, travoprost, bimatoprost, and unoprostone isopropyl. In the event the therapeutic agent selected is anionic in an aqueous solution at an ophthalmically acceptable pH level, the amounts of zinc and borate or borate/polyol buffers required to self-preserve such compositions may need to be increased somewhat, due to interactions between the therapeutic agent and zinc ions.

The present invention is particularly directed to the provision of self-preserved, multi-dose ophthalmic compositions in connection with the treatment of conditions wherein the cornea or adjacent ocular tissues are irritated, or conditions requiring frequent application of a composition, such as in the treatment of dry eye patients. The self-preserved compositions of the present invention are therefore particularly useful in the field of artificial tears, ocular lubricants, and other compositions used to treat dry eye conditions, as well as other conditions involving ocular inflammation or discomfort.

The ophthalmic compositions of the present invention may be formulated to include one or more agents to enhance ocular comfort and/or retention of the compositions on the eye following topical application. The types of agents which may be utilized include: cellulose derivatives, such as hydroxypropyl methylcellulose ("HPMC"); Dextran 70; polyethylene glycol; propylene glycol; carboxy vinyl polymers; polyvinyl alcohol polymers or copolymers; and polysaccharides. The preferred polysaccharides are hydroxypropyl guar and other galactomannan polymers described in U.S. Patent No. 6,583,125 (Asgharian). The entire contents of the '125 patent are hereby incorporated in the present specification by reference.

Some of the agents described in the preceding paragraph (e.g., hydroxypropyl guar, referred to hereinafter as "hp-guar") are capable of forming complexes with borate. The formation of such complexes may hamper the antimicrobial activity of the borate/amino alcohol system described herein. In the event such interference is encountered, adjustments to the system may be required. For example, the borate concentration can be increased, but this may result in an undesirable increase in the viscosity of the composition. The present invention is based in-part on a finding that the adverse impact of such polymers on the antimicrobial activity of the borate/amino alcohol system can be overcome by including zinc in the compositions.

The compositions of the present invention will generally be formulated as sterile aqueous solutions. The compositions of the present invention will be formulated so as to be compatible with the eye and/or other tissues to be treated with the compositions. The ophthalmic compositions intended for direct application to the eye will be formulated so as to have a pH and tonicity which are compatible with the eye. A buffer may be required so as to maintain the pH of the compositions with a range of 6.0 to 8.5, and may require a tonicity agent to bring the osmolality of the composition to a level at or near 210-350 milliosmoles per kilogram (mOsm/kg).

One or more conventional antimicrobial preservatives (e.g., benzalkonium chloride and polyquaternium-1) can be present in the compositions of the present invention, if desired, but the compositions preferably do not contain any conventional antimicrobial preservatives. If utilized, such preservatives can be present in conventional amounts, but in view of the self-preserving properties of the compositions of the present invention, such conventional antimicrobial preservatives can also be utilized in much lower concentrations than would be required to satisfy preservative efficacy requirements if only the conventional antimicrobial preservative were present in amounts less than conventional amounts. Since the present compositions can be a self-preserved composition, if an anti-microbial preservative is present as an option, the amount can be an amount that would not be effective alone as an antimicrobial preservative agent. However, the overall composition would have sufficient antimicrobial activity to satisfy USP/FDA/ISO preservative efficacy requirements.

Preferably the conventional antimicrobial preservative, if present, is not anionic and if anionic, it is preferred that the amount should be low enough to not substantially interfere with the antimicrobial activity of the preservative systems described herein.

Applicants specifically incorporate the entire contents of all cited references in this disclosure. Further, when an amount, concentration, or other value or parameter is given as either a range, preferred range, or a list of upper preferable values and lower preferable values, this is to be understood as specifically disclosing all ranges formed from any pair of any upper range limit or preferred value and any lower range limit or preferred value, regardless of whether ranges are separately disclosed. Where a range of numerical values is recited herein, unless otherwise stated, the range is intended to include the endpoints thereof, and all integers and fractions within the range. It is not intended that the scope of the invention be limited to the specific values recited when defining a range.

Other embodiments of the present invention will be apparent to those skilled in the art from consideration of the present specification and practice of the present invention disclosed herein. It is intended that the present specification and examples be considered as exemplary only with a true scope and spirit of the invention being indicated by the following claims and equivalents thereof.

The following examples are presented to further illustrate selected embodiments of the present invention.

Example 1

The formulation shown in Table 1 below was prepared to evaluate the effect of a pH of 7.9 on the antimicrobial activity of the formulation.

Table 1

Component	FID 103777 Lot Number 17110-01
	Concentration (w/v %)
Dextran 70	0.1
HPMC	0.3
Propylene Glycol	0.3
Boric acid	0.8
Sorbitol	1.4
Sodium chloride	0.1
Potassium chloride	0.12
Calcium chloride	0.0053
Magnesium chloride	0.0064
Zinc chloride	0.00015
AMP (95%)	0.588
pH	7.9

The formulation described in Table 1 was prepared as follows:

HPMC Solution:

1. In a 250mL Pyrex media bottle, add the correct amount of 2% HPMC stock solution.
2. Autoclave at 121°C for 30 minutes.
3. Hold the autoclaved solution for later compounding.

Buffer Vehicle:

1. In a 250mL beaker, add the remaining formulation chemicals for a 200mL batch using only 150mL of purified water.
2. Measure the pH and adjust to 7.9 with NaOH/HCl.
3. QS to 100% (150mL) with purified water.
4. Filter the solution using a 0.2μm CA filter unit.

Final Formulation:

1. Slowly add the filtered buffer vehicle to the autoclaved HPMC stock solution.
2. Allow the solution to mix well.

The antimicrobial activity of the above-described solution was evaluated by means of a standard microbiological analysis (i.e., USP26 Antimicrobial Effectiveness Test). The test samples were challenged with standardized suspensions of five microorganisms, and the number of surviving microorganisms was determined at 7, 14 and 28 days. The results are presented in Table 2 below:

Table 2

Microorganism	Time (days)	Log_{10} Reduction of Survivors Lot Number 17110-01
A. niger	7	2.0
	14	2.1
	28	2.9
C. albicans	7	0.4
	14	1.4
	28	3.0
E. coli	7	2.2
	14	5.1
	28	5.1
P. aeruginosa	7	2.5
	14	5.0
	28	5.0
S. aureus	7	2.1
	14	4.6
	28	4.8

The results demonstrate overall preservative efficacy against the organisms tested.

Example 2

As explained above, polymers that are capable of forming complexes with borates (e.g., guar or hp-guar) have been found to reduce the antimicrobial activity of the borate/amino alcohol systems described herein. The formulation shown in Table 3 below is similar to the formulation described in Example 1, except that Dextran 70 and HPMC have been replaced by hp-guar.

A formulation nearly identical to the one shown in Table 3 was evaluated to determine if it had adequate antimicrobial activity to satisfy USP preservative efficacy requirements. It was determined that inclusion of hp-guar prevented the formulation from consistently satisfying the USP preservative efficacy requirements. However, it was discovered that this problem could be overcome by increasing the concentration of zinc chloride by a factor of 10 (i.e., from 0.00015 to 0.0015 w/v %). The formulation shown in Table 3, which contains this higher concentration of zinc chloride, has consistently satisfied the USP preservative efficacy requirements. The preservative efficacy test ("PET") results for four different lots are provided below:

Table 3

Formulation Number FID 105783/Concentration (w/v %)

	FID 105783
Component	
HP-Guar	0.16
Boric Acid	0.7
Sorbitol	1.4
PEG-400	0.4
Propylene Glycol	0.3
Potassium Chloride	0.12
Sodium Chloride	0.1
Calcium Chloride	0.0053
Magnisium Chloride	0.0064
Zinc Chloride	0.0015
AMP (95%)	0.57
Hydrochloric Acid	Adj. pH
Target pH	7.9
Purified Water	QS to 100%
Volume to make (L)	1

PET Results				
Lot Number	**PD Lot**	**03-34508**	**03-34433**	**03-34632**
P.aeruginosa (Day 7)	5.0	5.0	4.8	5.0
E.coli (Day 7)	5.0	5.0	4.9	5.0
P.aeruginosa (Day 14)	5.0	5.0	4.8	5.0
E.coli (Day 14)	5.0	5.0	4.9	5.0
P.aeruginosa (Day 28)	3.9*	3.9*	4.8	ND
E.coli (Day 28)	4.0*	4.0*	4.9	ND

*Rechallenge on day 14

**ND = Not Performed

Example 3

The formulations shown in Tables 4 and 5 below were prepared and tested in order to evaluate the effect of small variations in pH on the antimicrobial activity of the compositions.

Table 4
Effect of pH

	Formulation Number/Concentrations (w/v %)			
	FID 105784	**FID 105801**	**FID 105802**	**FID 105782**
Batch/Lot	**03-34662**	**03-34667**	**03-34669**	**03-34648**
Component				
HP-Guar	0.16	0.16	0.16	0.16
Boric Acid	0.7	0.7	0.7	0.7
Sorbitol	1.4	1.4	1.4	1.4
PEG-400	0.4	0.4	0.4	0.4
Propylene Glycol	0.3	0.3	0.3	0.3
Potassium Chloride	0.12	0.12	0.12	0.12
Sodium Chloride	0.1	0.1	0.1	0.1
Calcium Chloride	0.0053	0.0053	0.0053	0.0053
Magnisium Chloride	0.0064	0.0064	0.0064	0.0064
Zinc Chloride	0.00075	0.00075	0.00075	0.00075
AMP (95%)	0.6	0.6	0.6	0.6
Hydrochloric Acid	Adj. pH	Adj. pH	Adj. pH	Adj. pH
Target pH	7.0	7.3	7.6	7.9
Purified Water	QS to 100%	QS to 100%	QS to 100%	QS to 100%
Volume to make (L)	1	1	1	1
PET Results (Day 7)				
P.aeruginosa	-0.5	-0.6	-0.2	2.1
E.coli	-0.5	0.1	3.3	5.0

The results presented in Table 4 show that as the pH of the formula is increased, the activity against the test organisms consistently improved. At a pH of 7.9, the composition satisfied the USP 26 preservative efficacy requirements. However, the compositions having a pH of less than 7.9 did not have adequate antimicrobial activity to satisfy the USP requirements.

The antimicrobial activities of two formulations that were identical except for pH were also compared.. As shown in Table 5 below, the formulation having a pH of 7.7 did not satisfy USP 26 preservative efficacy requirements, but the formulation having a pH of 7.9 did meet those requirements.

Table 5

Effect of pH

Component	Concentration (w/v %)	Concentration (w/v %)
HP-Guar	0.16	0.16
Boric Acid	0.7	0.7
Sorbitol	1.4	1.4
PEG-400	0.4	0.4
Propylene Glycol	0.3	0.3
Potassium Chloride	0.12	0.12
Sodium Chloride	0.1	0.1
Calcium Chloride	0.0053	0.0053
Magnesium Chloride	0.0064	0.0064
Zinc Chloride	0.0015	0.0015
AMP (95%)	0.6	0.6
HCl/Adjust pH to	7.9	7.7
Purified Water	QS 100	QS 100
Microbiology	Passes USP	Fails USP

Example 4

The formulations shown in Table 6 below were prepared in order to evaluate the effect of zinc chloride on antimicrobial activity. The first two solutions, which contained no zinc and 1.5 ppm of zinc chloride, respectively, did not satisfy the USP 26 preservative efficacy requirements, but the third solution, which contained 15 ppm of zinc chloride, did meet those requirements.

Table 6
Effect of Zinc Level

	Formulation Number/Concentrations (w/v %)		
	FID 105689	**FID 104706**	**FID 105688**
Batch/Lot	**03-34434**	**03-34405**	**03-34433**
Component			
HP-Guar	0.16	0.16	0.16
Boric Acid	0.7	0.7	0.7
PEG-400	0.4	0.4	0.4
Propylene Glycol	0.3	0.3	0.3
Sorbitol	1.4	1.4	1.4
Sodium Chloride	0.1	0.1	0.1
Potassium Chloride	0.12	0.12	0.12
Calcium Chloride	0	0.0053	0.0053
Magnisium Chloride	0	0.0064	0.0064
Zinc Chloride	0	0.00015	0.0015
AMP (95%)	0.6	0.6	0.6
Hydrochloric Acid	Adj. pH	Adj. pH	Adj. pH
Target pH	7.9	7.9	7.9
Purified Water	QS to 100%	QS to 100%	QS to 100%
PET Results (Day 7)			
P.aeruginosa	2.6	0.7	4.8
E.coli	0.9	1.8	4.9

Example 5

The effect of zinc chloride on antimicrobial activity was further investigated by evaluating the preservative efficacy of the solutions shown in Table 7 below. The zinc chloride concentrations evaluated were 1.5 ppm, 3.0 ppm, 3.5 ppm, 7.5 ppm and 15 ppm, respectively. The results presented at the bottom of Table 7 show greater antimicrobial activity with increasing concentrations of zinc chloride. At 15 ppm, the two test organisms were totally eliminated (i.e., no survivors).

Table 7
Effect of Zinc Levels

	Formulation Number/Concentration (w/v %)				
	FID 104706	**FID 105780**	**FID 105792**	**FID 105782**	**FID 105783**
Batch/Lot	**03-34628**	**03-34629**	**03-34652**	**03-34648**	**03-34632**
Component					
HP-Guar	0.16	0.16	0.16	0.16	0.16
Boric Acid	0.7	0.7	0.7	0.7	0.7
Sorbitol	1.4	1.4	1.4	1.4	1.4
PEG-400	0.4	0.4	0.4	0.4	0.4
Propylene Glycol	0.3	0.3	0.3	0.3	0.3
Potassium Chloride	0.12	0.12	0.12	0.12	0.12
Sodium Chloride	0.1	0.1	0.1	0.1	0.1
Calcium Chloride	0.0053	0.0053	0.0053	0.0053	0.0053
Magnisium Chloride	0.0064	0.0064	0.0064	0.0064	0.0064
Zinc Chloride	0.00015	0.0003	0.00045	0.00075	0.0015
AMP (95%)	0.6	0.6	0.6	0.6	0.6
Hydrochloric Acid	Adj. pH	Adj. pH	Adj. pH	Adj. pH	Adj. pH
Target pH	7.9	7.9	7.9	7.9	7.9
Purified Water	QS to 100%	QS to 100%	QS to 100%	QS to 100%	QS to 100%
PET Results (Day 7)					
P.aeruginosa	1.4	1.5	1.3	2.1	5.0
E.coli	1.0	2.1	3.9	5.0	5.0

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Example 6

The role of amino alcohol concentration relative to antimicrobial activity was also investigated. The formulations shown in Table 8 below, which were identical except for the concentration of the amino alcohol AMP (95%), were utilized in this evaluation. As shown at the bottom of Table 8, the solutions containing AMP (95%) at concentrations of 0.2 and 0.4 w/v % did not satisfy the USP 26 preservative efficacy requirements against *Pseudomonas aeruginosa*, but the solution containing AMP (95%) at a concentration of 0.6 w/v % did meet those requirements.

Table 8
Amino Alcohol Concentration

	Formulation Number/Concentration (w/v %)		
	FID 105799	**FID 105800**	**FID 105782**
Batch/Lot	**03-34665**	**03-34666**	**03-34648**
Component	**Conc. (%)**	**Conc. (%)**	**Conc. (%)**
HP-Guar	0.16	0.16	0.16
Boric Acid	0.7	0.7	0.7
Sorbitol	1.4	1.4	1.4
PEG-400	0.4	0.4	0.4
Propylene Glycol	0.3	0.3	0.3
Potassium Chloride	0.12	0.12	0.12
Sodium Chloride	0.1	0.1	0.1
Calcium Chloride	0.0053	0.0053	0.0053
Magnisium Chloride	0.0064	0.0064	0.0064
Zinc Chloride	0.00075	0.00075	0.00075
AMP (95%)	0.2	0.4	0.6
Hydrochloric Acid	Adj. pH	Adj. pH	Adj. pH
Target pH	7.9	7.9	7.9
Purified Water	QS to 100%	QS to 100%	QS to 100%
Volume to make (L)	1	1	1
PET Results (Day 7)			
P.aeruginosa	-0.7	-0.2	2.1
E.coli	5.0	4.9	5.0

Example 7

The above-described preservative system was also evaluated relative to ophthalmic formulations containing the therapeutic agents travoprost and patanol, respectively. The results of show that these compositions are projected to satisfy preservative efficacy requirements.

Table 9

COMPONENT	% w/v	% w/v	% w/v	% w/v	% w/v	% w/v	% w/v
AL6221	0.004	0.004	0.004	0.004	0.004	0.004	0.004
Polyoxyl 40 HCO	0.5	0.5	0.5	0.5	0.5	0.5	0.75
Zinc Chloride	0.0025	0.0025	0.0025	0.0025	0.0025	0.0025	0.0025
Boric Acid	1	1	1	1	1	1	1
Sorbitol	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Propylene Glycol	0	0.25	0.5	0.75	0.75	0.75	0.25
NaOH/HCl q.s. pH	6.0	6.0	6.0	6.0	6.0	6.0	6.0
Purified Water q.s. 100%	100	100	100	100	100	100	100
Osmolality	176	214	248	272	282	282	214
6 Hr. and 24 Hr. Staph A.	-	-	-	-	-	0.0 & 0.1	-
6 and 24 Hr. Pseudomonas	-	-	-	-	-	1.2 & 2.3	-
6 Hr. and 24 Hr. E. Coli	-	-	-	-	-	1.0 & 1.5	-
7 Day Staph A.	2.6	4.9	4.9	5.0	4.4	4.9	4.9
7 Day Pseudomonas A.	4.6	5.0	5.0	4.0	5.1	5.1	5.0
7 Day E. Coli	2.7	2.7	2.3	3.2 [d]	2.6	2.7	3.0
7 Day Candida A.	0.1	0.0	0.2	0.2	0.2	0.2	0.0
7 Day A. Niger	2.2	2.6	2.6	1.8	2.8	2.3	2.9

Example 8

The results obtained with the formulations shown below demonstrate the role of zinc concentration.

Table 10

FID Number	**FID 105937**	**FID 105935**	**FID 105926**	**FID 105936**
Bacth/Lot	**03-34915**	**03-34913**	**03-34904**	**03-34914**
AL-12355 (HP-8A Guar)	0.16	0.16	0.16	0.16
Boric Acid	1.0	1.0	1.0	1.0
PEG-400	0.4	0.4	0.4	0.4
Propylene Glycol	0.3	0.3	0.3	0.3
Potassium Chloride	0.13	0.13	0.13	0.13
Calcium Chloride	0.0053	0.0053	0.0053	0.0053
Magnesium Chloride	0.0064	0.0064	0.0064	0.0064
Zinc Chloride	N/A	0.00075	0.0015	0.00225
Sodium Hydroxide	Adj. pH	Adj. pH	Adj. pH	Adj. pH
Tris	N/A	N/A	N/A	N/A
Hydrochloric Acid	Adj. pH	Adj. pH	Adj. pH	Adj. pH
Target pH	7.4	7.4	7.4	7.4
Purified Water	QS to 100%	QS to 100%	QS to 100%	QS to 100%
7 days P. aeruginosa	0.6	2.1	3.9	3.2
7 days E. coli	0.1	3.1	5.0	5.0
14 days P. aeruginosa	N/A	2.9	5.1	4.3
14 days E. coli	N/A	3.4	5.0	5.0
28 days P. aeruginosa	N/A	N/A	5.1	5.1
28 days E. coli	N/A	N/A	5.0	5.0

Example 9

The following formulations further illustrate the efficacy of preservative systems containing zinc and borate/polyol complexes.

Table 11

FID Number	FID 105973	FID 105974	FID 105975	FID 105976	FID 105977	FID 105978
Bacth/Lot	**03-34977**	**03-34978**	**03-34979**	**03-34980**	**03-34981**	**03-34982**
Boric Acid	1.0	1.0	1.0	1.0	1.0	1.0
Propylene Glycol	0.4	0.4	0.4	0.4	0.4	0.4
Zinc Chloride	0.0015	0.0015	0.0015	0.0015	0.0015	0.0015
Polyoxyl 40 Hydrogenated Castor Oil	0.5	0.05	0.5	0.5	0.5	0.5
Disodium EDTA	N/A	0.05	0.05	N/A	0.05	0.05
Polyquad	N/A	N/A	0.001	N/A	N/A	0.001
Tromethamine	Adj. pH	Adj. pH	Adj. pH	Adj. pH	Adj. pH	Adj. pH
Hydrochloric Acid	Adj. pH	Adj. pH	Adj. pH	Adj. pH	Adj. pH	Adj. pH
Target pH	6.0	6.0	6.0	6.0	6.0	6.0
Purified Water	QS to 100%	QS to 100%	QS to 100%	QS to 100%	QS to 100%	QS to 100%
7 days P. aeruginosa	5.1	5.1	5.1	5.1	5.1	5.1
7 days E. coli	3.3	1.6	4.9	3.9	0.6	4.9
14 days P. aeruginosa	5.1	5.1	5.1	5.1	NT	5.1
14 days E. coli	4.9	1.9	4.9	4.9	NT	4.9

NT=Not tested due to Day 7 Failure

ID Number	FID 105982	FID 105983	FID 105984	FID 105985	FID 105986
Bacth/Lot	**03-034988**	**03-034989**	**03-34990**	**03-34991**	**03-34992**
Boric Acid	1.0	1.0	1.0	1.0	1.0
Propylene Glycol	0.4	0.4	0.4	0.4	0.4
Zinc Chloride	0.0015	0.0015	0.0015	0.0015	0.0015
Polyoxyl 40 Stearate	0.1	0.1	0.1	0.1	0.1
Sodium Hydroxide	N/A	N/A	N/A	Adj. pH	Adj. pH
Hydrochloric Acid	Adj. pH	Adj. pH	Adj. pH	Adj. pH	Adj. pH
Target pH	7.4	7.55	7.7	7.4	7.55
Purified Water	QS to 100%	QS to 100%	QS to 100%	QS to 100%	QS to 100%
7 days P. aeruginosa	4.9	4.9	4.9	4.9	4.9
7 days E. coli	4.3	3.8	3.9	4.9	4.9
14 days P. aeruginosa	4.9	4.9	4.9	4.9	4.9
14 days E. coli	4.9	4.9	4.9	4.9	4.9

We Claim:

1. A multi-dose, self-preserved ophthalmic composition, said composition comprising an antimicrobial effective amount of a preservative system comprising 0.5 to 6.0 wt.% of a borate/polyol complex and zinc ions at a concentration of 0.000017 to 0.00017 moles per liter.

2. A composition according to Claim 1, wherein the zinc ions are provided in the form of zinc chloride at a concentration of from 0.0005 to 0.005 w/v %.

3. A composition according to Claim 1, wherein the composition is an aqueous ophthalmic solution having sufficient antimicrobial activity to satisfy USP preservative efficacy requirements.

4. A composition according to Claim 1, wherein the composition does not contain a conventional antimicrobial preservative.

5. A composition according to Claim 1, further comprising at least one therapeutically active agent.

6. A method of enhancing the antimicrobial activity of an aqueous ophthalmic pharmaceutical composition, which comprises including an antimicrobial effective amount of a preservative system comprising 0.5 to 6.0 wt.% of a borate/polyol complex and zinc ions at a concentration of 0.000017 to 0.00017 moles per liter.

7. A method according to Claim 6, wherein the zinc ions are provided in the form of zinc chloride at a concentration of from 0.0005 to 0.005 w/v %.

8. A method according to Claim 6, wherein the composition is a multi-dose, self-preserved ophthalmic solution having sufficient antimicrobial activity to satisfy USP preservative efficacy requirements.

9. A method according to Claim 8, wherein the composition does not contain a conventional antimicrobial agent.

10. A method according to Claim 6, wherein the composition contains a least one therapeutically active agent.

Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	SELF-PRESERVED AQUEOUS PHARMACEUTICAL COMPOSITIONS
First Named Inventor/Applicant Name:	Masood A. Chowhan
Filer:	Scott Chapple/Barbara McKenzie
Attorney Docket Number:	2667 US F

Filed as Large Entity

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Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
National Stage Fee	1631	1	330	330
Natl Stage Search Fee - Report provided	1642	1	430	430
National Stage Exam - all other cases	1633	1	220	220
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**980**

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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal of New Application	2667_US_F_371Transmittal_031909.pdf	143133 2cd516380515a377f2feb24be87fdaa6d5955b4a	no	3
Warnings:					
Information:					
2	Preliminary Amendment	2667_US_F_PrelimAmend_031909.pdf	24186 b54901bd608851df8de382c7952d227d3fd7fdcf	no	1
Warnings:					
Information:					
3	Oath or Declaration filed	2667_US_F_Decl_031907.pdf	97500 6814c74967b73baec273c96f12b881c4e28620a0	no	3
Warnings:					
Information:					
4	Documents submitted with 371 Applications	PCT-2007-079094_IPER.pdf	167772 bcc6cb9a9a94b0990fd0954ecc14b249cb94caf6	no	4
Warnings:					
Information:					
5	Documents submitted with 371 Applications	PCT-2007-079094_SearchRpt.pdf	286618 108d2c583fd5c6feaea7e3e13b98f55ab46b6a01	no	6
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6	Documents submitted with 371 Applications	WO_2008_042619_A2.pdf	1230684 16ffa5658f3d6c93e53275b8b9cbfb5ed6c224fc	no	31
Warnings:					
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7	Fee Worksheet (PTO-06)	fee-info.pdf	33338 bf1dcbf6a1881bcac352c911c4fe136209589eb2	no	2
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(71) Applicant *(for all designated States except US)*: **ALCON MANUFACTURING, LTD.** [US/US]; 6201 South Freeway, Mail Code TB4-8, Fort Worth, Texas 76134-2099 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **CHOWHAN, Masood A.** [US/US]; 3521 Lake Tahoe Dr., Arlington, Texas 76016 (US). **KEITH, David, J.** [US/US]; 508 Millcreek Lane, Washington, Missouri 63090 (US).

(74) Agents: **BROWN, Gregg C.** et al.; 6201 South Freeway, Mail Code TB4-8, Fort Worth, Texas 76134-2099 (US).

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(54) Title: SELF-PRESERVED AQUEOUS PHARMACEUTICAL COMPOSITIONS

(57) Abstract: The use of a borate/polyol and zinc system to enhance the antimicrobial activity of multi-dose pharmaceutical compositions is described. The compositions do not require a conventional anti-microbial preservative and therefore are referred to as being 'self-preserved'. The compositions possess sufficient antimicrobial activity to satisfy the preservative efficacy requirements of the USP for aqueous ophthalmic compositions.

SELF-PRESERVED AQUEOUS PHARMACEUTICAL COMPOSITIONS

Background of the Invention

The present invention is directed to self-preserved pharmaceutical compositions. More specifically, the invention is directed to the provision of aqueous, multi-dose pharmaceutical compositions that have been formulated so as to have sufficient antimicrobial activity to satisfy the preservation efficacy requirements of the United States Pharmacopeia ("USP") and analogous guidelines in other countries, without requiring a conventional antimicrobial preservative, such as benzalkonium chloride, polyquaternium-1, hydrogen peroxide (e.g., sodium perborate), or chorine-containing agents. The ability to achieve self-preservation is based on a unique combination of formulation components and criteria.

Many pharmaceutical compositions are required to be sterile (i.e., free of bacteria, fungi and other pathogenic microorganisms). Examples of such compositions include: solutions and suspensions that are injected into the bodies of humans or other mammals; creams, lotions, solutions or other preparations that are topically applied to wounds, abrasions, burns, rashes, surgical incisions, or other conditions where the skin is not intact; and various types of compositions that are applied either directly to the eye (e.g., artificial tears, irrigating solutions, and drug products), or are applied to devices that will come into contact with the eye (e.g., contact lenses).

The foregoing types of compositions can be manufactured under sterile conditions via procedures that are well known to those skilled in the art. However, once the packaging for a product is opened, such that the composition contained therein is exposed to the atmosphere and other sources of potential microbial contamination (e.g., the hands of a human patient), the sterility of the product may be

compromised. Such products are typically utilized multiple times by the patient, and are therefore frequently referred to as being of a "multi-dose" nature.

Due to the frequent, repeated exposure of multi-dose products to the risk of microbial contamination, it is necessary to employ a means for preventing such contamination from occurring. The means employed may be: (i) a chemical agent that prevents the proliferation of microbes in a composition, which is referred to herein as an "antimicrobial preservative"; or (ii) a packaging system that prevents or reduces the risk of microbes reaching a pharmaceutical composition within a container.

Prior multi-dose ophthalmic compositions have generally contained one or more antimicrobial preservations in order to prevent the proliferation of bacteria, fungi and other microbes. Such compositions may come into contact with the cornea either directly or indirectly. The cornea is particularly sensitive to exogenous chemical agents. Consequently, in order to minimize the potential for harmful effects on the cornea, it is preferable to use anti-microbial preservatives that are relatively non-toxic to the cornea, and to use such preservatives at the lowest possible concentrations (i.e., the minimum amounts required in order to perform their anti-microbial functions).

Balancing the anti-microbial efficacy and potential toxicological effects of anti-microbial preservatives is sometimes difficult to achieve. More specifically, the concentration of an antimicrobial agent necessary for the preservation of ophthalmic formulations from microbial contamination may create the potential for toxicological effects on the cornea and/or other ophthalmic tissues. Using lower concentrations of the anti-microbial agents generally helps to reduce the potential for such toxicological effects, but the lower concentrations may be insufficient to achieve the required level of biocidal efficacy (i.e., antimicrobial preservation).

The use of an inadequate level of antimicrobial preservation may create the potential for microbial contamination of the compositions and ophthalmic infections resulting from such contaminations. This is also a serious problem, since ophthalmic infections involving *Pseudomonas aeruginosa* or other virulent microorganisms can lead to loss of visual function or even loss of the eye.

Thus, there is a need for a means of enhancing the activity of anti-microbial agents so that very low concentrations of the agents can be utilized without increasing the potential for toxicological effects or subjecting patients to unacceptable risks of microbial contamination and resulting ophthalmic infections.

Ophthalmic compositions are generally formulated as isotonic, buffered solutions. One approach to enhancing the anti-microbial activity of such compositions is to include multi-functional components in the compositions. In addition to performing their primary functions, these multi-functional components also serve to enhance the overall anti-microbial activity of the compositions.

The following publications may be referred to for further background regarding the use of multi-functional components to enhance the antimicrobial activity of ophthalmic compositions:

1. U.S. Patent No. 5,817,277 (Mowrey-McKee, et al; tromethamine);
2. U.S. Patent No. 6,503,497 (Chowhan, et al.; borate/polyol complexes);
3. U.S. Patent No. 5,741,817 (Chowhan, et al.; low molecular weight amino acids such as glycine);
4. U.S. Patent No. 6,319,464 (Asgharian; low molecular weight amino alcohols); and
5. U.S. Patent Application Publication No. US 2002/0122831 A1 (Mowrey-McKee, et al.; bis-aminopolyols).

The present invention is also based in-part on a finding that zinc further enhances the antimicrobial activity of ophthalmic compositions containing borate/polyol complexes of the type described herein. The use of zinc to enhance the antimicrobial activity of pharmaceutical compositions, including ophthalmic solutions, is well known. See, for example, the following articles and patent publications, as well as U.S. Patent No. 6,348,190 and JP 2003-104870, cited above:

McCarthy, "Metal Ions and Microbial Inhibitors", Cosmetic & Toiletries, 100:69-72 (Feb. 1985);

Zeelie, et al., "The Effects of Selected Metal Salts on the Microbial Activities of Agents used in the Pharmaceutical and Related Industries", Metal Compounds in Environment and Life, 4:193-200 (1992);

Zeelie, et al., "Effects of Copper and Zinc Ions on the Germicidal Properties of Two Popular Pharmaceutical Antiseptic Agents, Cetylpyridinium Chloride and Povidone-iodine", Analyst, 123:503-507 (March 1998);

McCarthy, et al., "The Effect of Zinc Ions on the Antimicrobial Activity of Selected Preservatives", Journal of Pharmacy and Pharmacology, Vol. 41 (1989);

U.S. Patent No. 6,482,799 (Tuśe, et al.);

U.S. Patent No. 5,320,843 (Raheja, et al.);

U.S. Patent No. 5,221,664 (Berkowitz, et al.);

U.S. Patent No. 6,034,043 (Fujiwara, et al.);

U.S. Patent No. 4,522,806 (Muhlemann, et al.);

U.S. Patent No. 6,017,861 (Fujiwara, et al.); and

U.S. Patent No. 6,121,315 (Nair, et al.).

However, the use of zinc ions in combination with borate/polyol complexes, as described herein is not disclosed or suggested by the prior art.

The compositions of the present invention are multi-dose products that do not contain a conventional antimicrobial preservative (e.g., benzalkonium chloride), but yet are preserved from microbial contamination. Such compositions have been referred to in the art as being "preservative free" (see, e.g., U.S. Patent No. 5,597,559 issued to Olejnik, et al.). Compositions that are preserved from microbial contamination as a result of the inherent antimicrobial activity of one or more components of the compositions are also referred to in the art as being "self-preserved" (see, e.g., U.S. Patent No. 6,492,361 issued to Muller, et al.).

The following publication may be referred to for further background regarding pharmaceutical compositions that are "preservative-free" or "self-preserving": Kabara, et al., Preservative-Free and Self-Preserving Cosmetics and Drugs – Principles and Practice, Chapter 1, pages 1-14, Marcel Dekker, Inc. (1997).

The multi-dose compositions of the present invention, which do not contain a conventional antimicrobial preservative are referred to herein as being "self-preserved".

Summary of the Invention

The present invention is based on a finding that zinc is capable of enhancing the antimicrobial activity of aqueous pharmaceutical compositions containing

borate/polyol complexes, when utilized as described herein, so as to create aqueous, multi-dose compositions that satisfy the preservative efficacy requirements of the USP without a conventional antimicrobial preservative.

The self-preserved, multi-dose compositions of the present invention have several advantages over existing ophthalmic formulations that are either: (i) packaged as a "single dose" or "unit of use" product, so as to avoid the inclusion of any antimicrobial preservative (e.g., BION®TEARS Lubricant Eye Drops, which is marketed by Alcon Laboratories, Inc.), or (ii) preserved by means of a so-called "disappearing" preservatives, such as the chlorite-based system described in U.S. Patent Nos. 5,424,078; 5,736,165; 6,024,954; and 5,858,346 (e.g., the artificial tears product "REFRESH™ Tears", which is marketed by Allergan), or the peroxide-containing system described in U.S. Patent Nos. 5,607,698; 5,683,993; 5,725,887; and 5,858,996 (e.g., the artificial tear product "GenTeal™ Tears", which is marketed by CIBAVision).

Unlike these existing products, the multi-dose ophthalmic compositions of the present invention are able to satisfy the USP preservative efficacy requirements without employing any conventional antimicrobial preservatives, such as chlorite or hydrogen peroxide.

The above-discussed findings regarding the zinc may be applied to enhance the antimicrobial activity of various types of pharmaceutical compositions. However, the present invention is particularly directed to the provision of aqueous ophthalmic solutions that are effective in preventing microbial contamination in the absence of conventional antimicrobial preservatives, such as benzalkonium chloride ("BAC"), polyquaternium-1, chlorite or hydrogen peroxide.

Detailed Description of the Invention

The pharmaceutical compositions of the present invention contain a borate/polyol complex and zinc ions in amounts sufficient to enhance the antimicrobial activity of the compositions, such that a conventional antimicrobial preservative is not required.

As used herein, the term "borate" includes boric acid, salts of boric acid, other pharmaceutically acceptable borates, and combinations thereof. The following borates are particularly preferred: boric acid, sodium borate, potassium borate and combinations thereof. The use of borates containing divalent cations (e.g., calcium borate) may adversely affect the antimicrobial action of zinc ions, by competing with zinc for binding sites on the cell walls of bacterial and other microbes, and is therefore not preferred. For the same reason, the self-preserved compositions of the present invention are preferably free of or substantially free of other sources of divalent cations, such as calcium chloride.

As used herein, the term "polyol" includes any compound having at least one hydroxyl group on each of two adjacent carbon atoms that are not in *trans* configuration relative to each other. The polyols can be linear or cyclic, substituted or unsubstituted, or mixtures thereof, so long as the resultant complex is water soluble and pharmaceutically acceptable. Examples of such compounds include: sugars, sugar alcohols, sugar acids and uronic acids. Preferred polyols are sugars, sugar alcohols and sugar acids, including, but not limited to: mannitol, glycerin, xylitol, sorbitol and propylene glycol. The use of sorbitol, propylene glycol, or a combination thereof is particularly preferred.

The self-preserved compositions of the present invention preferably contain one or more borates in an amount of from about 0.1 to about 2.0% w/v, more preferably 0.3 to 1.5% w/v, and most preferably 0.5 to 1.2% w/v. The compositions of the present invention preferably contain one or more polyols in an amount of from about 0.01 to about 5.0% w/v, more preferably 0.6 to 2.0% w/v.

The use of borate-polyol complexes to enhance antimicrobial activity is described in U.S. Patent No. 6,503,497 (Chowhan, et al.), the entire contents of which are hereby incorporated in the present specification by reference. The above-described borate/polyol complexes are utilized in the compositions of the present invention in an amount effective to enhance the antimicrobial activity of the composition. The total concentration of the borate/polyol complex will typically be in the range of 0.5 to 6.0 percent by weight ("wt.%").

The zinc may be provided in various forms, such as zinc chloride, zinc sulfate, zinc acetate or zinc carbonate. The use of zinc chloride is preferred. The amount of zinc chloride required to achieve this effect may vary somewhat from formulation to formulation, depending on the particular borate/polyol complex selected, but will generally be from about 0.0005% to about 0.005% w/v, preferably 0.00075 to 0.0025% w/v.

In general, the self-preserved compositions of the present invention will preferably contain zinc, either in the form of zinc chloride or other zinc salts, at a molar concentration of 0.000017 moles/liter to 0.00017 moles/liter, preferably 0.000026 moles/liter to 0.00009 moles/liter. However, the concentration of zinc may be as high as 0.0035 moles/liter.

The manner in which zinc enhances antimicrobial activity in the compositions of the present invention is not completely understood. However, it is believed that zinc atoms enhance the antimicrobial activity of borates by forming bridges between the borate groups

The present invention is particularly directed to the provision of multi-dose, self-preserved ophthalmic compositions that contain zinc and borate in amounts sufficient to allow the compositions to satisfy the USP preservative efficacy requirements, as well as other preservative efficacy standards for aqueous pharmaceutical compositions, without a conventional antimicrobial preservative.

Relative to bacteria, the USP 27 Antimicrobial Effectiveness Test requires that multi-dose ophthalmic compositions have sufficient antimicrobial activity to reduce an initial inoculum of approximately 10^5 to 10^6 bacteria by one log (i.e., a 90% reduction in the microorganism population) over a period of seven (7) days and by three logs (i.e., a 99.9% reduction in the microorganism population) over a period of fourteen (14) days, and requires that there cannot be any increase in the microorganism population following the conclusion of the fourteen day period. Relative to fungi, the USP standards require that the compositions maintain stasis (i.e., no growth) relative to the population of the initial inoculum over the entire 28 day test period. The margin of error in calculating microorganism populations is generally accepted to be 0.5 logs. Accordingly, the term "stasis" as utilized relative to the above-discussed USP standards means that the initial fungi population cannot increase by more than 0.5 log orders, relative to the initial population.

The preservative efficacy standards for multi-dose ophthalmic solutions in the U.S. and other countries/regions are set forth in the following table:

Preservative Efficacy Test ("PET") Criteria

(Log Order Reduction of Microbial Inoculum Over Time

	Bacteria	Fungi
USP 27	A reduction of 1 log (90%), by day 7; 3 logs (99.9%) by day 14; and no increase after day 14	The compositions must demonstrate over the entire test period, which means no increases of 0.5 logs or greater, relative to the initial inoculum.
Japan	3 logs by 14 days; and no increase from day 14 through day 28.	No increase from initial count at 14 and 28 days
Ph. Eur. A[1]	A reduction of 2 logs (99%) by 6 hours; 3 logs by 24 hours; and no recovery after 28 days	A reduction of 2 logs (99%) by 7 days, and no increase thereafter
Ph. Eur. B	A reduction of 1 log at 24 hours; 3 logs by day 7; and no increase thereafter	A reduction of 1 log (90%) by day 14, and no increase thereafter
FDA/ISO 14730	A reduction of 3 logs from initial challenge at day 14; and a reduction of 3 logs from rechallenge	No increase higher than the initial value at day 14, and no increase higher than the day 14 rechallenge count through day 28.

[1]There are two preservative efficacy standards in the European Pharmacopoeia ' "A" and "B".

The standards identified above for the USP 27 are substantially identical to the requirements set forth in prior editions of the USP, particularly USP 24, USP 25 and USP 26.

The compositions of the present invention may also include one or more low molecular weight amino alcohols. The amino alcohols which may be utilized in the present invention are water-soluble and have a molecular weight in the range of from about 60 to about 200. The following compounds are representative of the low molecular weight amino alcohols which may be utilized in the present invention: 2-amino-2-methyl-1-propanol (AMP), 2-dimethylamino-methyl-1-propanol (DMAMP),

2-amino-2-ethyl-1,3-propanediol (AEPD), 2-amino-2-methyl-1,3-propanediol (AMPD), 2-amino-1-butanol (AB). "AMP (95%)", which refers to 95% pure AMP and 5% water, is the most preferred low molecular weight amino alcohol of the present invention. These amino alcohols are available commercially from Angus Chemical Company (Buffalo Grove, Illinois).

The amount of amino alcohol used will depend on the molecular weight of the amino alcohol selected, and the presence (or absence) of other ingredients in the composition (e.g., chelating agents, buffering agents and/or tonicity agents). The amino alcohol will generally be present in an amount necessary to enhance the antimicrobial activity of an aqueous self-preserved pharmaceutical composition of the type described herein. The amount of amino alcohol required for a particular composition can be determined through comparative testing, such as the tests described in Example 6 hereof. The above-described amino alcohols are also utilized in the compositions of the present invention to neutralize the pH of the borate or borate/polyol complex, or bring the composition to the desired pH level. The amount of amino alcohol required for this purpose is a function of the particular borate or borate/polyol mixture selected and the concentration thereof. In general, the self-preserved compositions of the present invention will contain one or more amino alcohols at a total concentration of from about 0.01 to about 2.0 percent by weight/volume ("%w/v"), and preferably from 0.1 to 1.0 %w/v.

The zinc and borate/polyol preservative systems described herein may be included in various types of pharmaceutical compositions to enhance anti-microbial activity and self-preserve the compositions, such as ophthalmic, otic, nasal and dermatological compositions, but is particularly useful in ophthalmic compositions. Examples of such compositions include: ophthalmic pharmaceutical compositions, such as topical compositions used in the treatment of glaucoma, infections, allergies or inflammation; compositions for treating contact lenses, such as cleaning products and products for enhancing the ocular comfort of patients wearing contact lenses; and

various other types of ophthalmic compositions, such as ocular lubricating products, artificial tears, astringents, and so on. The compositions may be aqueous or non-aqueous, but will generally be aqueous.

The ophthalmic pharmaceutical compositions of the present invention may contain various types of therapeutic agents. Examples of possible therapeutic agents include beta-blockers (e.g., timolol, betaxolol, levobetaxolol, carteolol, levobunolol, and propranolol), carbonic anhydrase inhibitors (e.g., brinzolamide and dorzolamide), alpha-1 antagonists (e.g., nipradolol), alpha-2 agonists (e.g. iopidine and brimonidine), miotics (e.g., pilocarpine and epinephrine), prostaglandin analogs (e.g., latanoprost, travoprost and unoprostone), hypotensive lipids (e.g., bimatoprost and compounds set forth in U.S. Pat. No. 5,352,708), neuroprotectants (e.g., memantine), serotonergics [e.g., 5-HT_2 agonists, such as S-(+)-1-(2-aminopropyl)-indazole-6-ol)], anti-angiogenesis agents (e.g., anecortave acetate), anti-infective agents (e.g., quinolones, such as moxifloxacin and gatifloxacin, and aminoglycosides, such as tobramycin and gentamicin), non-steroidal and steroidal anti-inflammatory agents (e.g., prednisolone, dexamethasone, lotoprednol, suprofen, diclofenac and ketorolac), growth factors (e.g., EGF), immunosuppressant agents (e.g., cyclosporin), and anti-allergic agents (e.g., olopatadine). The ophthalmic drug may be present in the form of a pharmaceutically acceptable salt, such as timolol maleate, brimonidine tartrate or sodium diclofenac. The compositions of the present invention may also include combinations of ophthalmic drugs, such as combinations of (i) a beta-blocker selected from the group consisting of betaxolol and timolol, and (ii) a prostaglandin analog selected from the group consisting of latanoprost, 1, 5-keto latanoprost, travoprost, bimatoprost, and unoprostone isopropyl. In the event the therapeutic agent selected is anionic in an aqueous solution at an ophthalmically acceptable pH level, the amounts of zinc and borate or borate/polyol buffers required to self-preserve such compositions may need to be increased somewhat, due to interactions between the therapeutic agent and zinc ions.

The present invention is particularly directed to the provision of self-preserved, multi-dose ophthalmic compositions in connection with the treatment of conditions wherein the cornea or adjacent ocular tissues are irritated, or conditions requiring frequent application of a composition, such as in the treatment of dry eye patients. The self-preserved compositions of the present invention are therefore particularly useful in the field of artificial tears, ocular lubricants, and other compositions used to treat dry eye conditions, as well as other conditions involving ocular inflammation or discomfort.

The ophthalmic compositions of the present invention may be formulated to include one or more agents to enhance ocular comfort and/or retention of the compositions on the eye following topical application. The types of agents which may be utilized include: cellulose derivatives, such as hydroxypropyl methylcellulose ("HPMC"); Dextran 70; polyethylene glycol; propylene glycol; carboxy vinyl polymers; polyvinyl alcohol polymers or copolymers; and polysaccharides. The preferred polysaccharides are hydroxypropyl guar and other galactomannan polymers described in U.S. Patent No. 6,583,125 (Asgharian). The entire contents of the '125 patent are hereby incorporated in the present specification by reference.

Some of the agents described in the preceding paragraph (e.g., hydroxypropyl guar, referred to hereinafter as "hp-guar") are capable of forming complexes with borate. The formation of such complexes may hamper the antimicrobial activity of the borate/amino alcohol system described herein. In the event such interference is encountered, adjustments to the system may be required. For example, the borate concentration can be increased, but this may result in an undesirable increase in the viscosity of the composition. The present invention is based in-part on a finding that the adverse impact of such polymers on the antimicrobial activity of the borate/amino alcohol system can be overcome by including zinc in the compositions.

The compositions of the present invention will generally be formulated as sterile aqueous solutions. The compositions of the present invention will be formulated so as to be compatible with the eye and/or other tissues to be treated with the compositions. The ophthalmic compositions intended for direct application to the eye will be formulated so as to have a pH and tonicity which are compatible with the eye. A buffer may be required so as to maintain the pH of the compositions with a range of 6.0 to 8.5, and may require a tonicity agent to bring the osmolality of the composition to a level at or near 210-350 milliosmoles per kilogram (mOsm/kg).

One or more conventional antimicrobial preservatives (e.g., benzalkonium chloride and polyquaternium-1) can be present in the compositions of the present invention, if desired, but the compositions preferably do not contain any conventional antimicrobial preservatives. If utilized, such preservatives can be present in conventional amounts, but in view of the self-preserving properties of the compositions of the present invention, such conventional antimicrobial preservatives can also be utilized in much lower concentrations than would be required to satisfy preservative efficacy requirements if only the conventional antimicrobial preservative were present in amounts less than conventional amounts. Since the present compositions can be a self-preserved composition, if an anti-microbial preservative is present as an option, the amount can be an amount that would not be effective alone as an antimicrobial preservative agent. However, the overall composition would have sufficient antimicrobial activity to satisfy USP/FDA/ISO preservative efficacy requirements.

Preferably the conventional antimicrobial preservative, if present, is not anionic and if anionic, it is preferred that the amount should be low enough to not substantially interfere with the antimicrobial activity of the preservative systems described herein.

Applicants specifically incorporate the entire contents of all cited references in this disclosure. Further, when an amount, concentration, or other value or parameter is given as either a range, preferred range, or a list of upper preferable values and lower preferable values, this is to be understood as specifically disclosing all ranges formed from any pair of any upper range limit or preferred value and any lower range limit or preferred value, regardless of whether ranges are separately disclosed. Where a range of numerical values is recited herein, unless otherwise stated, the range is intended to include the endpoints thereof, and all integers and fractions within the range. It is not intended that the scope of the invention be limited to the specific values recited when defining a range.

Other embodiments of the present invention will be apparent to those skilled in the art from consideration of the present specification and practice of the present invention disclosed herein. It is intended that the present specification and examples be considered as exemplary only with a true scope and spirit of the invention being indicated by the following claims and equivalents thereof.

The following examples are presented to further illustrate selected embodiments of the present invention.

Example 1

The formulation shown in Table 1 below was prepared to evaluate the effect of a pH of 7.9 on the antimicrobial activity of the formulation.

Table 1

Component	FID 103777 Lot Number 17110-01
	Concentration (w/v %)
Dextran 70	0.1
HPMC	0.3
Propylene Glycol	0.3
Boric acid	0.8
Sorbitol	1.4
Sodium chloride	0.1
Potassium chloride	0.12
Calcium chloride	0.0053
Magnesium chloride	0.0064
Zinc chloride	0.00015
AMP (95%)	0.588
pH	7.9

The formulation described in Table 1 was prepared as follows:

HPMC Solution:

1. In a 250mL Pyrex media bottle, add the correct amount of 2% HPMC stock solution.
2. Autoclave at 121°C for 30 minutes.
3. Hold the autoclaved solution for later compounding.

Buffer Vehicle:

1. In a 250mL beaker, add the remaining formulation chemicals for a 200mL batch using only 150mL of purified water.
2. Measure the pH and adjust to 7.9 with NaOH/HCl.
3. QS to 100% (150mL) with purified water.
4. Filter the solution using a 0.2μm CA filter unit.

Final Formulation:

1. Slowly add the filtered buffer vehicle to the autoclaved HPMC stock solution.
2. Allow the solution to mix well.

The antimicrobial activity of the above-described solution was evaluated by means of a standard microbiological analysis (i.e., USP26 Antimicrobial Effectiveness Test). The test samples were challenged with standardized suspensions of five microorganisms, and the number of surviving microorganisms was determined at 7, 14 and 28 days. The results are presented in Table 2 below:

Table 2

Microorganism	Time (days)	Log_{10} Reduction of Survivors Lot Number 17110-01
A. niger	7	2.0
	14	2.1
	28	2.9
C. albicans	7	0.4
	14	1.4
	28	3.0
E. coli	7	2.2
	14	5.1
	28	5.1
P. aeruginosa	7	2.5
	14	5.0
	28	5.0
S. aureus	7	2.1
	14	4.6
	28	4.8

The results demonstrate overall preservative efficacy against the organisms tested.

Example 2

As explained above, polymers that are capable of forming complexes with borates (e.g., guar or hp-guar) have been found to reduce the antimicrobial activity of the borate/amino alcohol systems described herein. The formulation shown in Table 3 below is similar to the formulation described in Example 1, except that Dextran 70 and HPMC have been replaced by hp-guar.

A formulation nearly identical to the one shown in Table 3 was evaluated to determine if it had adequate antimicrobial activity to satisfy USP preservative efficacy requirements. It was determined that inclusion of hp-guar prevented the formulation from consistently satisfying the USP preservative efficacy requirements. However, it was discovered that this problem could be overcome by increasing the concentration of zinc chloride by a factor of 10 (i.e., from 0.00015 to 0.0015 w/v %). The formulation shown in Table 3, which contains this higher concentration of zinc chloride, has consistently satisfied the USP preservative efficacy requirements. The preservative efficacy test ("PET") results for four different lots are provided below:

Table 3

Formulation Number FID 105783/Concentration (w/v %)

	FID 105783
Component	
HP-Guar	0.16
Boric Acid	0.7
Sorbitol	1.4
PEG-400	0.4
Propylene Glycol	0.3
Potassium Chloride	0.12
Sodium Chloride	0.1
Calcium Chloride	0.0053
Magnisium Chloride	0.0064
Zinc Chloride	0.0015
AMP (95%)	0.57
Hydrochloric Acid	Adj. pH
Target pH	7.9
Purified Water	QS to 100%
Volume to make (L)	1

PET Results				
Lot Number	**PD Lot**	**03-34508**	**03-34433**	**03-34632**
P.aeruginosa (Day 7)	5.0	5.0	4.8	5.0
E.coli (Day 7)	5.0	5.0	4.9	5.0
P.aeruginosa (Day 14)	5.0	5.0	4.8	5.0
E.coli (Day 14)	5.0	5.0	4.9	5.0
P.aeruginosa (Day 28)	3.9*	3.9*	4.8	ND
E.coli (Day 28)	4.0*	4.0*	4.9	ND

*Rechallenge on day 14

**ND = Not Performed

Example 3

The formulations shown in Tables 4 and 5 below were prepared and tested in order to evaluate the effect of small variations in pH on the antimicrobial activity of the compositions.

Table 4
Effect of pH

	Formulation Number/Concentrations (w/v %)			
	FID 105784	**FID 105801**	**FID 105802**	**FID 105782**
Batch/Lot	**03-34662**	**03-34667**	**03-34669**	**03-34648**
Component				
HP-Guar	0.16	0.16	0.16	0.16
Boric Acid	0.7	0.7	0.7	0.7
Sorbitol	1.4	1.4	1.4	1.4
PEG-400	0.4	0.4	0.4	0.4
Propylene Glycol	0.3	0.3	0.3	0.3
Potassium Chloride	0.12	0.12	0.12	0.12
Sodium Chloride	0.1	0.1	0.1	0.1
Calcium Chloride	0.0053	0.0053	0.0053	0.0053
Magnisium Chloride	0.0064	0.0064	0.0064	0.0064
Zinc Chloride	0.00075	0.00075	0.00075	0.00075
AMP (95%)	0.6	0.6	0.6	0.6
Hydrochloric Acid	Adj. pH	Adj. pH	Adj. pH	Adj. pH
Target pH	7.0	7.3	7.6	7.9
Purified Water	QS to 100%	QS to 100%	QS to 100%	QS to 100%
Volume to make (L)	1	1	1	1
PET Results (Day 7)				
P.aeruginosa	-0.5	-0.6	-0.2	2.1
E.coli	-0.5	0.1	3.3	5.0

The results presented in Table 4 show that as the pH of the formula is increased, the activity against the test organisms consistently improved. At a pH of 7.9, the composition satisfied the USP 26 preservative efficacy requirements. However, the compositions having a pH of less than 7.9 did not have adequate antimicrobial activity to satisfy the USP requirements.

The antimicrobial activities of two formulations that were identical except for pH were also compared.. As shown in Table 5 below, the formulation having a pH of 7.7 did not satisfy USP 26 preservative efficacy requirements, but the formulation having a pH of 7.9 did meet those requirements.

Table 5

Effect of pH

Component	Concentration (w/v %)	Concentration (w/v %)
HP-Guar	0.16	0.16
Boric Acid	0.7	0.7
Sorbitol	1.4	1.4
PEG-400	0.4	0.4
Propylene Glycol	0.3	0.3
Potassium Chloride	0.12	0.12
Sodium Chloride	0.1	0.1
Calcium Chloride	0.0053	0.0053
Magnesium Chloride	0.0064	0.0064
Zinc Chloride	0.0015	0.0015
AMP (95%)	0.6	0.6
HCl/Adjust pH to	7.9	7.7
Purified Water	QS 100	QS 100
Microbiology	Passes USP	Fails USP

Example 4

The formulations shown in Table 6 below were prepared in order to evaluate the effect of zinc chloride on antimicrobial activity. The first two solutions, which contained no zinc and 1.5 ppm of zinc chloride, respectively, did not satisfy the USP 26 preservative efficacy requirements, but the third solution, which contained 15 ppm of zinc chloride, did meet those requirements.

Table 6
Effect of Zinc Level

	Formulation Number/Concentrations (w/v %)		
	FID 105689	**FID 104706**	**FID 105688**
Batch/Lot	**03-34434**	**03-34405**	**03-34433**
Component			
HP-Guar	0.16	0.16	0.16
Boric Acid	0.7	0.7	0.7
PEG-400	0.4	0.4	0.4
Propylene Glycol	0.3	0.3	0.3
Sorbitol	1.4	1.4	1.4
Sodium Chloride	0.1	0.1	0.1
Potassium Chloride	0.12	0.12	0.12
Calcium Chloride	0	0.0053	0.0053
Magnisium Chloride	0	0.0064	0.0064
Zinc Chloride	0	0.00015	0.0015
AMP (95%)	0.6	0.6	0.6
Hydrochloric Acid	Adj. pH	Adj. pH	Adj. pH
Target pH	7.9	7.9	7.9
Purified Water	QS to 100%	QS to 100%	QS to 100%
PET Results (Day 7)			
P.aeruginosa	2.6	0.7	4.8
E.coli	0.9	1.8	4.9

Example 5

The effect of zinc chloride on antimicrobial activity was further investigated by evaluating the preservative efficacy of the solutions shown in Table 7 below. The zinc chloride concentrations evaluated were 1.5 ppm, 3.0 ppm, 3.5 ppm, 7.5 ppm and 15 ppm, respectively. The results presented at the bottom of Table 7 show greater antimicrobial activity with increasing concentrations of zinc chloride. At 15 ppm, the two test organisms were totally eliminated (i.e., no survivors).

Table 7
Effect of Zinc Levels

	Formulation Number/Concentration (w/v %)				
	FID 104706	**FID 105780**	**FID 105792**	**FID 105782**	**FID 105783**
Batch/Lot	**03-34628**	**03-34629**	**03-34652**	**03-34648**	**03-34632**
Component					
HP-Guar	0.16	0.16	0.16	0.16	0.16
Boric Acid	0.7	0.7	0.7	0.7	0.7
Sorbitol	1.4	1.4	1.4	1.4	1.4
PEG-400	0.4	0.4	0.4	0.4	0.4
Propylene Glycol	0.3	0.3	0.3	0.3	0.3
Potassium Chloride	0.12	0.12	0.12	0.12	0.12
Sodium Chloride	0.1	0.1	0.1	0.1	0.1
Calcium Chloride	0.0053	0.0053	0.0053	0.0053	0.0053
Magnisium Chloride	0.0064	0.0064	0.0064	0.0064	0.0064
Zinc Chloride	0.00015	0.0003	0.00045	0.00075	0.0015
AMP (95%)	0.6	0.6	0.6	0.6	0.6
Hydrochloric Acid	Adj. pH	Adj. pH	Adj. pH	Adj. pH	Adj. pH
Target pH	7.9	7.9	7.9	7.9	7.9
Purified Water	QS to 100%	QS to 100%	QS to 100%	QS to 100%	QS to 100%
PET Results (Day 7)					
P.aeruginosa	1.4	1.5	1.3	2.1	5.0
E.coli	1.0	2.1	3.9	5.0	5.0

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Example 6

The role of amino alcohol concentration relative to antimicrobial activity was also investigated. The formulations shown in Table 8 below, which were identical except for the concentration of the amino alcohol AMP (95%), were utilized in this evaluation. As shown at the bottom of Table 8, the solutions containing AMP (95%) at concentrations of 0.2 and 0.4 w/v % did not satisfy the USP 26 preservative efficacy requirements against *Pseudomonas aeruginosa*, but the solution containing AMP (95%) at a concentration of 0.6 w/v % did meet those requirements.

Table 8
Amino Alcohol Concentration

	Formulation Number/Concentration (w/v %)		
	FID 105799	**FID 105800**	**FID 105782**
Batch/Lot	**03-34665**	**03-34666**	**03-34648**
Component	**Conc. (%)**	**Conc. (%)**	**Conc. (%)**
HP-Guar	0.16	0.16	0.16
Boric Acid	0.7	0.7	0.7
Sorbitol	1.4	1.4	1.4
PEG-400	0.4	0.4	0.4
Propylene Glycol	0.3	0.3	0.3
Potassium Chloride	0.12	0.12	0.12
Sodium Chloride	0.1	0.1	0.1
Calcium Chloride	0.0053	0.0053	0.0053
Magnisium Chloride	0.0064	0.0064	0.0064
Zinc Chloride	0.00075	0.00075	0.00075
AMP (95%)	0.2	0.4	0.6
Hydrochloric Acid	Adj. pH	Adj. pH	Adj. pH
Target pH	7.9	7.9	7.9
Purified Water	QS to 100%	QS to 100%	QS to 100%
Volume to make (L)	1	1	1
PET Results (Day 7)			
P.aeruginosa	-0.7	-0.2	2.1
E.coli	5.0	4.9	5.0

Example 7

The above-described preservative system was also evaluated relative to ophthalmic formulations containing the therapeutic agents travoprost and patanol, respectively. The results of show that these compositions are projected to satisfy preservative efficacy requirements.

Table 9

COMPONENT	% w/v	% w/v	% w/v	% w/v	% w/v	% w/v	% w/v
AL6221	0.004	0.004	0.004	0.004	0.004	0.004	0.004
Polyoxyl 40 HCO	0.5	0.5	0.5	0.5	0.5	0.5	0.75
Zinc Chloride	0.0025	0.0025	0.0025	0.0025	0.0025	0.0025	0.0025
Boric Acid	1	1	1	1	1	1	1
Sorbitol	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Propylene Glycol	0	0.25	0.5	0.75	0.75	0.75	0.25
NaOH/HCl q.s. pH	6.0	6.0	6.0	6.0	6.0	6.0	6.0
Purified Water q.s. 100%	100	100	100	100	100	100	100
Osmolality	176	214	248	272	282	282	214
6 Hr. and 24 Hr. Staph A.	-	-	-	-	-	0.0 & 0.1	-
6 and 24 Hr. Pseudomonas	-	-	-	-	-	1.2 & 2.3	-
6 Hr. and 24 Hr. E. Coli	-	-	-	-	-	1.0 & 1.5	-
7 Day Staph A.	2.6	4.9	4.9	5.0	4.4	4.9	4.9
7 Day Pseudomonas A.	4.6	5.0	5.0	4.0	5.1	5.1	5.0
7 Day E. Coli	2.7	2.7	2.3	3.2 [d]	2.6	2.7	3.0
7 Day Candida A.	0.1	0.0	0.2	0.2	0.2	0.2	0.0
7 Day A. Niger	2.2	2.6	2.6	1.8	2.8	2.3	2.9

Example 8

The results obtained with the formulations shown below demonstrate the role of zinc concentration.

Table 10

FID Number	**FID 105937**	**FID 105935**	**FID 105926**	**FID 105936**
Bacth/Lot	**03-34915**	**03-34913**	**03-34904**	**03-34914**
AL-12355 (HP-8A Guar)	0.16	0.16	0.16	0.16
Boric Acid	1.0	1.0	1.0	1.0
PEG-400	0.4	0.4	0.4	0.4
Propylene Glycol	0.3	0.3	0.3	0.3
Potassium Chloride	0.13	0.13	0.13	0.13
Calcium Chloride	0.0053	0.0053	0.0053	0.0053
Magnesium Chloride	0.0064	0.0064	0.0064	0.0064
Zinc Chloride	N/A	0.00075	0.0015	0.00225
Sodium Hydroxide	Adj. pH	Adj. pH	Adj. pH	Adj. pH
Tris	N/A	N/A	N/A	N/A
Hydrochloric Acid	Adj. pH	Adj. pH	Adj. pH	Adj. pH
Target pH	7.4	7.4	7.4	7.4
Purified Water	QS to 100%	QS to 100%	QS to 100%	QS to 100%
7 days P. aeruginosa	0.6	2.1	3.9	3.2
7 days E. coli	0.1	3.1	5.0	5.0
14 days P. aeruginosa	N/A	2.9	5.1	4.3
14 days E. coli	N/A	3.4	5.0	5.0
28 days P. aeruginosa	N/A	N/A	5.1	5.1
28 days E. coli	N/A	N/A	5.0	5.0

Example 9

The following formulations further illustrate the efficacy of preservative systems containing zinc and borate/polyol complexes.

Table 11

FID Number	FID 105973	FID 105974	FID 105975	FID 105976	FID 105977	FID 105978
Bacth/Lot	**03-34977**	**03-34978**	**03-34979**	**03-34980**	**03-34981**	**03-34982**
Boric Acid	1.0	1.0	1.0	1.0	1.0	1.0
Propylene Glycol	0.4	0.4	0.4	0.4	0.4	0.4
Zinc Chloride	0.0015	0.0015	0.0015	0.0015	0.0015	0.0015
Polyoxyl 40 Hydrogenated Castor Oil	0.5	0.05	0.5	0.5	0.5	0.5
Disodium EDTA	N/A	0.05	0.05	N/A	0.05	0.05
Polyquad	N/A	N/A	0.001	N/A	N/A	0.001
Tromethamine	Adj. pH	Adj. pH	Adj. pH	Adj. pH	Adj. pH	Adj. pH
Hydrochloric Acid	Adj. pH	Adj. pH	Adj. pH	Adj. pH	Adj. pH	Adj. pH
Target pH	6.0	6.0	6.0	6.0	6.0	6.0
Purified Water	QS to 100%	QS to 100%	QS to 100%	QS to 100%	QS to 100%	QS to 100%
7 days P. aeruginosa	5.1	5.1	5.1	5.1	5.1	5.1
7 days E. coli	3.3	1.6	4.9	3.9	0.6	4.9
14 days P. aeruginosa	5.1	5.1	5.1	5.1	NT	5.1
14 days E. coli	4.9	1.9	4.9	4.9	NT	4.9

NT=Not tested due to Day 7 Failure

ID Number	FID 105982	FID 105983	FID 105984	FID 105985	FID 105986
Bacth/Lot	**03-034988**	**03-034989**	**03-34990**	**03-34991**	**03-34992**
Boric Acid	1.0	1.0	1.0	1.0	1.0
Propylene Glycol	0.4	0.4	0.4	0.4	0.4
Zinc Chloride	0.0015	0.0015	0.0015	0.0015	0.0015
Polyoxyl 40 Stearate	0.1	0.1	0.1	0.1	0.1
Sodium Hydroxide	N/A	N/A	N/A	Adj. pH	Adj. pH
Hydrochloric Acid	Adj. pH	Adj. pH	Adj. pH	Adj. pH	Adj. pH
Target pH	7.4	7.55	7.7	7.4	7.55
Purified Water	QS to 100%	QS to 100%	QS to 100%	QS to 100%	QS to 100%
7 days P. aeruginosa	4.9	4.9	4.9	4.9	4.9
7 days E. coli	4.3	3.8	3.9	4.9	4.9
14 days P. aeruginosa	4.9	4.9	4.9	4.9	4.9
14 days E. coli	4.9	4.9	4.9	4.9	4.9

We Claim:

1. A multi-dose, self-preserved ophthalmic composition, said composition comprising an antimicrobial effective amount of a preservative system comprising 0.5 to 6.0 wt.% of a borate/polyol complex and zinc ions at a concentration of 0.000017 to 0.00017 moles per liter.

2. A composition according to Claim 1, wherein the zinc ions are provided in the form of zinc chloride at a concentration of from 0.0005 to 0.005 w/v %.

3. A composition according to Claim 1, wherein the composition is an aqueous ophthalmic solution having sufficient antimicrobial activity to satisfy USP preservative efficacy requirements.

4. A composition according to Claim 1, wherein the composition does not contain a conventional antimicrobial preservative.

5. A composition according to Claim 1, further comprising at least one therapeutically active agent.

6. A method of enhancing the antimicrobial activity of an aqueous ophthalmic pharmaceutical composition, which comprises including an antimicrobial effective amount of a preservative system comprising 0.5 to 6.0 wt.% of a borate/polyol complex and zinc ions at a concentration of 0.000017 to 0.00017 moles per liter.

7. A method according to Claim 6, wherein the zinc ions are provided in the form of zinc chloride at a concentration of from 0.0005 to 0.005 w/v %.

8. A method according to Claim 6, wherein the composition is a multi-dose, self-preserved ophthalmic solution having sufficient antimicrobial activity to satisfy USP preservative efficacy requirements.

9. A method according to Claim 8, wherein the composition does not contain a conventional antimicrobial agent.

10. A method according to Claim 6, wherein the composition contains a least one therapeutically active agent.

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(71) Applicant *(for all designated States except US)*: **ALCON RESEARCH, LTD.** [US/US]; 6201 South Freeway, Mail Code TB4-8, Fort Worth, TX 76134 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **CHOWHAN, Masood A.** [US/US]; 3521 Lake Tahoe Dr., Arlington, Texas 76016 (US). **KEITH, David, J.** [US/US]; 508 Millcreek Lane, Washington, Missouri 63090 (US).

(74) Agents: **BROWN, Gregg C.** et al.; Alcon Research, Ltd., 6201 South Freeway MS TB4-8, Fort Worth, Texas 76134-2099 (US).

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Title of Invention	SELF-PRESERVED AQUEOUS PHARMACEUTICAL COMPOSITIONS	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
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Applicant 1 Remove

Applicant Authority ◉ Inventor ○ Legal Representative under 35 U.S.C. 117 ○ Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
	Masood	A.	CHOWHAN	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Arlington	State/Province	TX	Country of Residence [i]	US

Citizenship under 37 CFR 1.41(b) [i] US

Mailing Address of Applicant:

Address 1	3521 Lake Tahoe Drive		
Address 2			
City	Arlington	State/Province	TX
Postal Code	76016	Country [i]	US

Applicant 2 Remove

Applicant Authority ◉ Inventor ○ Legal Representative under 35 U.S.C. 117 ○ Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
	David	J.	KEITH	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Fort Worth	State/Province	TX	Country of Residence [i]	US

Citizenship under 37 CFR 1.41(b) [i] US

Mailing Address of Applicant:

Address 1	8004 Dusty Way		
Address 2			
City	Fort Worth	State/Province	TX
Postal Code	76123	Country [i]	US

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

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Suggested Class (if any)		**Sub Class (if any)**	
Suggested Technology Center (if any)			
Total Number of Drawing Sheets (if any)		**Suggested Figure for Publication (if any)**	

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ Request Not to Publish. I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application has not been and will not be the subject of an application filed in another country, or under a multilateral agreement, that requires publication at eighteen months after filing.

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Prior Application Status			Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)

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PTO/SB/14 (08-05)
Approved for use through 07/31/2006. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	2667Pr
	Application Number	
Title of Invention	SELF-PRESERVED AQUEOUS PHARMACEUTICAL COMPOSITIONS	

This section allows for the applicant to claim benefit of foreign priority and to identify any prior foreign application for which priority is not claimed. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55(a).

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Application Number	Country [i]	Parent Filing Date (YYYY-MM-DD)	Priority Claimed
			◉ Yes ○ No

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Assignee 1 Remove

If the Assignee is an Organization check here. ☑

Organization Name	ALCON MANUFACTURING, LTD.		
Mailing Address Information:			
Address 1	6201 South Freeway		
Address 2	Mail Code TB4-8		
City	Fort Worth	**State/Province**	TX
Country [i] US		Postal Code	76134
Phone Number	(817) 551-8663	Fax Number	(817) 551-4610
Email Address	gregg.brown@alconlabs.com		

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Signature	/Gregg C. Brown/			Date (YYYY-MM-DD)	2006-09-28
First Name	Gregg C.	Last Name	Brown	Registration Number	30613

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Docket No. 2667 US Pr **Electronically Filed**
September 28, 2006

SELF-PRESERVED AQUEOUS PHARMACEUTICAL COMPOSITIONS

Background of the Invention

The present invention is directed to self-preserved pharmaceutical compositions. More specifically, the invention is directed to the provision of aqueous, multi-dose pharmaceutical compositions that have been formulated so as to have sufficient antimicrobial activity to satisfy the preservation efficacy requirements of the United States Pharmacopeia ("USP") and analogous guidelines in other countries, without requiring a conventional antimicrobial preservative, such as benzalkonium chloride, polyquaternium-1, hydrogen peroxide (e.g., sodium perborate), or chorine-containing agents. The ability to achieve self-preservation is based on a unique combination of formulation components and criteria.

Many pharmaceutical compositions are required to be sterile (i.e., free of bacteria, fungi and other pathogenic microorganisms). Examples of such compositions include: solutions and suspensions that are injected into the bodies of humans or other mammals; creams, lotions, solutions or other preparations that are topically applied to wounds, abrasions, burns, rashes, surgical incisions, or other conditions where the skin is not intact; and various types of compositions that are applied either directly to the eye (e.g., artificial tears, irrigating solutions, and drug products), or are applied to devices that will come into contact with the eye (e.g., contact lenses).

The foregoing types of compositions can be manufactured under sterile conditions via procedures that are well known to those skilled in the art. However, once the packaging for a product is opened, such that the composition contained therein is exposed to the atmosphere and other sources of potential microbial contamination (e.g., the hands of a human patient), the sterility of the product may be

compromised. Such products are typically utilized multiple times by the patient, and are therefore frequently referred to as being of a "multi-dose" nature.

Due to the frequent, repeated exposure of multi-dose products to the risk of microbial contamination, it is necessary to employ a means for preventing such contamination from occurring. The means employed may be: (i) a chemical agent that prevents the proliferation of microbes in a composition, which is referred to herein as an "antimicrobial preservative"; or (ii) a packaging system that prevents or reduces the risk of microbes reaching a pharmaceutical composition within a container.

Prior multi-dose ophthalmic compositions have generally contained one or more antimicrobial preservations in order to prevent the proliferation of bacteria, fungi and other microbes. Such compositions may come into contact with the cornea either directly or indirectly. The cornea is particularly sensitive to exogenous chemical agents. Consequently, in order to minimize the potential for harmful effects on the cornea, it is preferable to use anti-microbial preservatives that are relatively non-toxic to the cornea, and to use such preservatives at the lowest possible concentrations (i.e., the minimum amounts required in order to perform their anti-microbial functions).

Balancing the anti-microbial efficacy and potential toxicological effects of anti-microbial preservatives is sometimes difficult to achieve. More specifically, the concentration of an antimicrobial agent necessary for the preservation of ophthalmic formulations from microbial contamination may create the potential for toxicological effects on the cornea and/or other ophthalmic tissues. Using lower concentrations of the anti-microbial agents generally helps to reduce the potential for such toxicological effects, but the lower concentrations may be insufficient to achieve the required level of biocidal efficacy (i.e., antimicrobial preservation).

The use of an inadequate level of antimicrobial preservation may create the potential for microbial contamination of the compositions and ophthalmic infections resulting from such contaminations. This is also a serious problem, since ophthalmic infections involving *Pseudomonas aeruginosa* or other virulent microorganisms can lead to loss of visual function or even loss of the eye.

Thus, there is a need for a means of enhancing the activity of anti-microbial agents so that very low concentrations of the agents can be utilized without increasing the potential for toxicological effects or subjecting patients to unacceptable risks of microbial contamination and resulting ophthalmic infections.

Ophthalmic compositions are generally formulated as isotonic, buffered solutions. One approach to enhancing the anti-microbial activity of such compositions is to include multi-functional components in the compositions. In addition to performing their primary functions, these multi-functional components also serve to enhance the overall anti-microbial activity of the compositions.

The following publications may be referred to for further background regarding the use of multi-functional components to enhance the antimicrobial activity of ophthalmic compositions:

1. U.S. Patent No. 5,817,277 (Mowrey-McKee, et al; tromethamine);
2. U.S. Patent No. 6,503,497 (Chowhan, et al.; borate/polyol complexes);
3. U.S. Patent No. 5,741,817 (Chowhan, et al.; low molecular weight amino acids such as glycine);
4. U.S. Patent No. 6,319,464 (Asgharian; low molecular weight amino alcohols); and
5. U.S. Patent Application Publication No. US 2002/0122831 A1 (Mowrey-McKee, et al.; bis-aminopolyols).

The present invention is also based in-part on a finding that zinc further enhances the antimicrobial activity of ophthalmic compositions containing borate/polyol complexes of the type described herein. The use of zinc to enhance the antimicrobial activity of pharmaceutical compositions, including ophthalmic solutions, is well known. See, for example, the following articles and patent publications, as well as U.S. Patent No. 6,348,190 and JP 2003-104870, cited above:

McCarthy, "Metal Ions and Microbial Inhibitors", Cosmetic & Toiletries, 100:69-72 (Feb. 1985);

Zeelie, et al., "The Effects of Selected Metal Salts on the Microbial Activities of Agents used in the Pharmaceutical and Related Industries", Metal Compounds in Environment and Life, 4:193-200 (1992);

Zeelie, et al., "Effects of Copper and Zinc Ions on the Germicidal Properties of Two Popular Pharmaceutical Antiseptic Agents, Cetylpyridinium Chloride and Povidone-iodine", Analyst, 123:503-507 (March 1998);

McCarthy, et al., "The Effect of Zinc Ions on the Antimicrobial Activity of Selected Preservatives", Journal of Pharmacy and Pharmacology, Vol. 41 (1989);

U.S. Patent No. 6,482,799 (Tuśe, et al.);

U.S. Patent No. 5,320,843 (Raheja, et al.);

U.S. Patent No. 5,221,664 (Berkowitz, et al.);

U.S. Patent No. 6,034,043 (Fujiwara, et al.);

U.S. Patent No. 4,522,806 (Muhlemann, et al.);

U.S. Patent No. 6,017,861 (Fujiwara, et al.); and

U.S. Patent No. 6,121,315 (Nair, et al.).

However, the use of zinc ions in combination with borate/polyol complexes, as described herein is not disclosed or suggested by the prior art.

The compositions of the present invention are multi-dose products that do not contain a conventional antimicrobial preservative (e.g., benzalkonium chloride), but yet are preserved from microbial contamination. Such compositions have been referred to in the art as being "preservative free" (see, e.g., U.S. Patent No. 5,597,559 issued to Olejnik, et al.). Compositions that are preserved from microbial contamination as a result of the inherent antimicrobial activity of one or more components of the compositions are also referred to in the art as being "self-preserved" (see, e.g., U.S. Patent No. 6,492,361 issued to Muller, et al.).

The following publication may be referred to for further background regarding pharmaceutical compositions that are "preservative-free" or "self-preserving": Kabara, et al., Preservative-Free and Self-Preserving Cosmetics and Drugs – Principles and Practice, Chapter 1, pages 1-14, Marcel Dekker, Inc. (1997).

The multi-dose compositions of the present invention, which do not contain a conventional antimicrobial preservative are referred to herein as being "self-preserved".

Summary of the Invention

The present invention is based on a finding that zinc is capable of enhancing the antimicrobial activity of aqueous pharmaceutical compositions containing

borate/polyol complexes, when utilized as described herein, so as to create aqueous, multi-dose compositions that satisfy the preservative efficacy requirements of the USP without a conventional antimicrobial preservative.

The self-preserved, multi-dose compositions of the present invention have several advantages over existing ophthalmic formulations that are either: (i) packaged as a "single dose" or "unit of use" product, so as to avoid the inclusion of any antimicrobial preservative (e.g., BION®TEARS Lubricant Eye Drops, which is marketed by Alcon Laboratories, Inc.), or (ii) preserved by means of a so-called "disappearing" preservatives, such as the chlorite-based system described in U.S. Patent Nos. 5,424,078; 5,736,165; 6,024,954; and 5,858,346 (e.g., the artificial tears product "REFRESH™ Tears", which is marketed by Allergan), or the peroxide-containing system described in U.S. Patent Nos. 5,607,698; 5,683,993; 5,725,887; and 5,858,996 (e.g., the artificial tear product "GenTeal™ Tears", which is marketed by CIBAVision).

Unlike these existing products, the multi-dose ophthalmic compositions of the present invention are able to satisfy the USP preservative efficacy requirements without employing any conventional antimicrobial preservatives, such as chlorite or hydrogen peroxide.

The above-discussed findings regarding the zinc may be applied to enhance the antimicrobial activity of various types of pharmaceutical compositions. However, the present invention is particularly directed to the provision of aqueous ophthalmic solutions that are effective in preventing microbial contamination in the absence of conventional antimicrobial preservatives, such as benzalkonium chloride ("BAC"), polyquaternium-1, chlorite or hydrogen peroxide.

Detailed Description of the Invention

The pharmaceutical compositions of the present invention contain a borate/polyol complex and zinc ions in amounts sufficient to enhance the antimicrobial activity of the compositions, such that a conventional antimicrobial preservative is not required.

As used herein, the term "borate" includes boric acid, salts of boric acid, other pharmaceutically acceptable borates, and combinations thereof. The following borates are particularly preferred: boric acid, sodium borate, potassium borate and combinations thereof. The use of borates containing divalent cations (e.g., calcium borate) may adversely affect the antimicrobial action of zinc ions, by competing with zinc for binding sites on the cell walls of bacterial and other microbes, and is therefore not preferred. For the same reason, the self-preserved compositions of the present invention are preferably free of or substantially free of other sources of divalent cations, such as calcium chloride.

As used herein, the term "polyol" includes any compound having at least one hydroxyl group on each of two adjacent carbon atoms that are not in *trans* configuration relative to each other. The polyols can be linear or cyclic, substituted or unsubstituted, or mixtures thereof, so long as the resultant complex is water soluble and pharmaceutically acceptable. Examples of such compounds include: sugars, sugar alcohols, sugar acids and uronic acids. Preferred polyols are sugars, sugar alcohols and sugar acids, including, but not limited to: mannitol, glycerin, xylitol, sorbitol and propylene glycol. The use of sorbitol, propylene glycol, or a combination thereof is particularly preferred.

The self-preserved compositions of the present invention preferably contain one or more borates in an amount of from about 0.1 to about 2.0% w/v, more preferably 0.3 to 1.5% w/v, and most preferably 0.5 to 1.2% w/v. The compositions of the present invention preferably contain one or more polyols in an amount of from about 0.01 to about 5.0% w/v, more preferably 0.6 to 2.0% w/v.

The use of borate-polyol complexes to enhance antimicrobial activity is described in U.S. Patent No. 6,503,497 (Chowhan, et al.), the entire contents of which are hereby incorporated in the present specification by reference. The above-described borate/polyol complexes are utilized in the compositions of the present invention in an amount effective to enhance the antimicrobial activity of the composition. The total concentration of the borate/polyol complex will typically be in the range of 0.5 to 6.0 percent by weight ("wt.%").

The zinc may be provided in various forms, such as zinc chloride, zinc sulfate, zinc acetate or zinc carbonate. The use of zinc chloride is preferred. The amount of zinc chloride required to achieve this effect may vary somewhat from formulation to formulation, depending on the particular borate/polyol complex selected, but will generally be from about 0.0005% to about 0.005% w/v, preferably 0.00075 to 0.0025% w/v.

In general, the self-preserved compositions of the present invention will preferably contain zinc, either in the form of zinc chloride or other zinc salts, at a molar concentration of 0.000017 moles/liter to 0.00017 moles/liter, preferably 0.000026 moles/liter to 0.00009 moles/liter. However, the concentration of zinc may be as high as 0.0035 moles/liter.

The manner in which zinc enhances antimicrobial activity in the compositions of the present invention is not completely understood. However, it is believed that zinc atoms enhance the antimicrobial activity of borates by forming bridges between the borate groups

The present invention is particularly directed to the provision of multi-dose, self-preserved ophthalmic compositions that contain zinc and borate in amounts sufficient to allow the compositions to satisfy the USP preservative efficacy requirements, as well as other preservative efficacy standards for aqueous pharmaceutical compositions, without a conventional antimicrobial preservative.

Relative to bacteria, the USP 27 Antimicrobial Effectiveness Test requires that multi-dose ophthalmic compositions have sufficient antimicrobial activity to reduce an initial inoculum of approximately 10^5 to 10^6 bacteria by one log (i.e., a 90% reduction in the microorganism population) over a period of seven (7) days and by three logs (i.e., a 99.9% reduction in the microorganism population) over a period of fourteen (14) days, and requires that there cannot be any increase in the microorganism population following the conclusion of the fourteen day period. Relative to fungi, the USP standards require that the compositions maintain stasis (i.e., no growth) relative to the population of the initial inoculum over the entire 28 day test period. The margin of error in calculating microorganism populations is generally accepted to be 0.5 logs. Accordingly, the term "stasis" as utilized relative to the above-discussed USP standards means that the initial fungi population cannot increase by more than 0.5 log orders, relative to the initial population.

The preservative efficacy standards for multi-dose ophthalmic solutions in the U.S. and other countries/regions are set forth in the following table:

Preservative Efficacy Test ("PET") Criteria

(Log Order Reduction of Microbial Inoculum Over Time

	Bacteria	Fungi
USP 27	A reduction of 1 log (90%), by day 7; 3 logs (99.9%) by day 14; and no increase after day 14	The compositions must demonstrate over the entire test period, which means no increases of 0.5 logs or greater, relative to the initial inoculum.
Japan	3 logs by 14 days; and no increase from day 14 through day 28.	No increase from initial count at 14 and 28 days
Ph. Eur. A[1]	A reduction of 2 logs (99%) by 6 hours; 3 logs by 24 hours; and no recovery after 28 days	A reduction of 2 logs (99%) by 7 days, and no increase thereafter
Ph. Eur. B	A reduction of 1 log at 24 hours; 3 logs by day 7; and no increase thereafter	A reduction of 1 log (90%) by day 14, and no increase thereafter
FDA/ISO 14730	A reduction of 3 logs from initial challenge at day 14; and a reduction of 3 logs from rechallenge	No increase higher than the initial value at day 14, and no increase higher than the day 14 rechallenge count through day 28.

[1]There are two preservative efficacy standards in the European Pharmacopoeia ' "A" and "B".

The standards identified above for the USP 27 are substantially identical to the requirements set forth in prior editions of the USP, particularly USP 24, USP 25 and USP 26.

The compositions of the present invention may also include one or more low molecular weight amino alcohols. The amino alcohols which may be utilized in the present invention are water-soluble and have a molecular weight in the range of from about 60 to about 200. The following compounds are representative of the low molecular weight amino alcohols which may be utilized in the present invention: 2-amino-2-methyl-1-propanol (AMP), 2-dimethylamino-methyl-1-propanol (DMAMP),

2-amino-2-ethyl-1,3-propanediol (AEPD), 2-amino-2-methyl-1,3-propanediol (AMPD), 2-amino-1-butanol (AB). "AMP (95%)", which refers to 95% pure AMP and 5% water, is the most preferred low molecular weight amino alcohol of the present invention. These amino alcohols are available commercially from Angus Chemical Company (Buffalo Grove, Illinois).

The amount of amino alcohol used will depend on the molecular weight of the amino alcohol selected, and the presence (or absence) of other ingredients in the composition (e.g., chelating agents, buffering agents and/or tonicity agents). The amino alcohol will generally be present in an amount necessary to enhance the antimicrobial activity of an aqueous self-preserved pharmaceutical composition of the type described herein. The amount of amino alcohol required for a particular composition can be determined through comparative testing, such as the tests described in Example 6 hereof. The above-described amino alcohols are also utilized in the compositions of the present invention to neutralize the pH of the borate or borate/polyol complex, or bring the composition to the desired pH level. The amount of amino alcohol required for this purpose is a function of the particular borate or borate/polyol mixture selected and the concentration thereof. In general, the self-preserved compositions of the present invention will contain one or more amino alcohols at a total concentration of from about 0.01 to about 2.0 percent by weight/volume ("%w/v"), and preferably from 0.1 to 1.0 %w/v.

The zinc and borate/polyol preservative systems described herein may be included in various types of pharmaceutical compositions to enhance anti-microbial activity and self-preserve the compositions, such as ophthalmic, otic, nasal and dermatological compositions, but is particularly useful in ophthalmic compositions. Examples of such compositions include: ophthalmic pharmaceutical compositions, such as topical compositions used in the treatment of glaucoma, infections, allergies or inflammation; compositions for treating contact lenses, such as cleaning products and products for enhancing the ocular comfort of patients wearing contact lenses; and

various other types of ophthalmic compositions, such as ocular lubricating products, artificial tears, astringents, and so on. The compositions may be aqueous or non-aqueous, but will generally be aqueous.

The ophthalmic pharmaceutical compositions of the present invention may contain various types of therapeutic agents. Examples of possible therapeutic agents include beta-blockers (e.g., timolol, betaxolol, levobetaxolol, carteolol, levobunolol, and propranolol), carbonic anhydrase inhibitors (e.g., brinzolamide and dorzolamide), alpha-1 antagonists (e.g., nipradolol), alpha-2 agonists (e.g. iopidine and brimonidine), miotics (e.g., pilocarpine and epinephrine), prostaglandin analogs (e.g., latanoprost, travoprost and unoprostone), hypotensive lipids (e.g., bimatoprost and compounds set forth in U.S. Pat. No. 5,352,708), neuroprotectants (e.g., memantine), serotonergics [e.g., 5-HT_2 agonists, such as S-(+)-1-(2-aminopropyl)-indazole-6-ol)], anti-angiogenesis agents (e.g., anecortave acetate), anti-infective agents (e.g., quinolones, such as moxifloxacin and gatifloxacin, and aminoglycosides, such as tobramycin and gentamicin), non-steroidal and steroidal anti-inflammatory agents (e.g., prednisolone, dexamethasone, lotoprednol, suprofen, diclofenac and ketorolac), growth factors (e.g., EGF), immunosuppressant agents (e.g., cyclosporin), and anti-allergic agents (e.g., olopatadine). The ophthalmic drug may be present in the form of a pharmaceutically acceptable salt, such as timolol maleate, brimonidine tartrate or sodium diclofenac. The compositions of the present invention may also include combinations of ophthalmic drugs, such as combinations of (i) a beta-blocker selected from the group consisting of betaxolol and timolol, and (ii) a prostaglandin analog selected from the group consisting of latanoprost, 1, 5-keto latanoprost, travoprost, bimatoprost, and unoprostone isopropyl. In the event the therapeutic agent selected is anionic in an aqueous solution at an ophthalmically acceptable pH level, the amounts of zinc and borate or borate/polyol buffers required to self-preserve such compositions may need to be increased somewhat, due to interactions between the therapeutic agent and zinc ions.

The present invention is particularly directed to the provision of self-preserved, multi-dose ophthalmic compositions in connection with the treatment of conditions wherein the cornea or adjacent ocular tissues are irritated, or conditions requiring frequent application of a composition, such as in the treatment of dry eye patients. The self-preserved compositions of the present invention are therefore particularly useful in the field of artificial tears, ocular lubricants, and other compositions used to treat dry eye conditions, as well as other conditions involving ocular inflammation or discomfort.

The ophthalmic compositions of the present invention may be formulated to include one or more agents to enhance ocular comfort and/or retention of the compositions on the eye following topical application. The types of agents which may be utilized include: cellulose derivatives, such as hydroxypropyl methylcellulose ("HPMC"); Dextran 70; polyethylene glycol; propylene glycol; carboxy vinyl polymers; polyvinyl alcohol polymers or copolymers; and polysaccharides. The preferred polysaccharides are hydroxypropyl guar and other galactomannan polymers described in U.S. Patent No. 6,583,125 (Asgharian). The entire contents of the '125 patent are hereby incorporated in the present specification by reference.

Some of the agents described in the preceding paragraph (e.g., hydroxypropyl guar, referred to hereinafter as "hp-guar") are capable of forming complexes with borate. The formation of such complexes may hamper the antimicrobial activity of the borate/amino alcohol system described herein. In the event such interference is encountered, adjustments to the system may be required. For example, the borate concentration can be increased, but this may result in an undesirable increase in the viscosity of the composition. The present invention is based in-part on a finding that the adverse impact of such polymers on the antimicrobial activity of the borate/amino alcohol system can be overcome by including zinc in the compositions.

The compositions of the present invention will generally be formulated as sterile aqueous solutions. The compositions of the present invention will be formulated so as to be compatible with the eye and/or other tissues to be treated with the compositions. The ophthalmic compositions intended for direct application to the eye will be formulated so as to have a pH and tonicity which are compatible with the eye. A buffer may be required so as to maintain the pH of the compositions with a range of 6.0 to 8.5, and may require a tonicity agent to bring the osmolality of the composition to a level at or near 210-350 milliosmoles per kilogram (mOsm/kg).

One or more conventional antimicrobial preservatives (e.g., benzalkonium chloride and polyquaternium-1) can be present in the compositions of the present invention, if desired, but the compositions preferably do not contain any conventional antimicrobial preservatives. If utilized, such preservatives can be present in conventional amounts, but in view of the self-preserving properties of the compositions of the present invention, such conventional antimicrobial preservatives can also be utilized in much lower concentrations than would be required to satisfy preservative efficacy requirements if only the conventional antimicrobial preservative were present in amounts less than conventional amounts. Since the present compositions can be a self-preserved composition, if an anti-microbial preservative is present as an option, the amount can be an amount that would not be effective alone as an antimicrobial preservative agent. However, the overall composition would have sufficient antimicrobial activity to satisfy USP/FDA/ISO preservative efficacy requirements.

Preferably the conventional antimicrobial preservative, if present, is not anionic and if anionic, it is preferred that the amount should be low enough to not substantially interfere with the antimicrobial activity of the preservative systems described herein.

Applicants specifically incorporate the entire contents of all cited references in this disclosure. Further, when an amount, concentration, or other value or parameter is given as either a range, preferred range, or a list of upper preferable values and lower preferable values, this is to be understood as specifically disclosing all ranges formed from any pair of any upper range limit or preferred value and any lower range limit or preferred value, regardless of whether ranges are separately disclosed. Where a range of numerical values is recited herein, unless otherwise stated, the range is intended to include the endpoints thereof, and all integers and fractions within the range. It is not intended that the scope of the invention be limited to the specific values recited when defining a range.

Other embodiments of the present invention will be apparent to those skilled in the art from consideration of the present specification and practice of the present invention disclosed herein. It is intended that the present specification and examples be considered as exemplary only with a true scope and spirit of the invention being indicated by the following claims and equivalents thereof.

The following examples are presented to further illustrate selected embodiments of the present invention.

Example 1

The formulation shown in Table 1 below was prepared to evaluate the effect of a pH of 7.9 on the antimicrobial activity of the formulation.

Table 1

Component	FID 103777 Lot Number 17110-01
	Concentration (w/v %)
Dextran 70	0.1
HPMC	0.3
Propylene Glycol	0.3
Boric acid	0.8
Sorbitol	1.4
Sodium chloride	0.1
Potassium chloride	0.12
Calcium chloride	0.0053
Magnesium chloride	0.0064
Zinc chloride	0.00015
AMP (95%)	0.588
pH	7.9

The formulation described in Table 1 was prepared as follows:

HPMC Solution:

1. In a 250mL Pyrex media bottle, add the correct amount of 2% HPMC stock solution.
2. Autoclave at 121°C for 30 minutes.
3. Hold the autoclaved solution for later compounding.

Buffer Vehicle:

1. In a 250mL beaker, add the remaining formulation chemicals for a 200mL batch using only 150mL of purified water.
2. Measure the pH and adjust to 7.9 with NaOH/HCl.
3. QS to 100% (150mL) with purified water.
4. Filter the solution using a 0.2µm CA filter unit.

Final Formulation:

1. Slowly add the filtered buffer vehicle to the autoclaved HPMC stock solution.
2. Allow the solution to mix well.

The antimicrobial activity of the above-described solution was evaluated by means of a standard microbiological analysis (i.e., USP26 Antimicrobial Effectiveness Test). The test samples were challenged with standardized suspensions of five microorganisms, and the number of surviving microorganisms was determined at 7, 14 and 28 days. The results are presented in Table 2 below:

Table 2

Microorganism	Time (days)	Log_{10} Reduction of Survivors Lot Number 17110-01
A. niger	7	2.0
	14	2.1
	28	2.9
C. albicans	7	0.4
	14	1.4
	28	3.0
E. coli	7	2.2
	14	5.1
	28	5.1
P. aeruginosa	7	2.5
	14	5.0
	28	5.0
S. aureus	7	2.1
	14	4.6
	28	4.8

The results demonstrate overall preservative efficacy against the organisms tested.

Example 2

As explained above, polymers that are capable of forming complexes with borates (e.g., guar or hp-guar) have been found to reduce the antimicrobial activity of the borate/amino alcohol systems described herein. The formulation shown in Table 3 below is similar to the formulation described in Example 1, except that Dextran 70 and HPMC have been replaced by hp-guar.

A formulation nearly identical to the one shown in Table 3 was evaluated to determine if it had adequate antimicrobial activity to satisfy USP preservative efficacy requirements. It was determined that inclusion of hp-guar prevented the formulation from consistently satisfying the USP preservative efficacy requirements. However, it was discovered that this problem could be overcome by increasing the concentration of zinc chloride by a factor of 10 (i.e., from 0.00015 to 0.0015 w/v %). The formulation shown in Table 3, which contains this higher concentration of zinc chloride, has consistently satisfied the USP preservative efficacy requirements. The preservative efficacy test ("PET") results for four different lots are provided below:

Table 3

Formulation Number FID 105783/Concentration (w/v %)

	FID 105783
Component	
HP-Guar	0.16
Boric Acid	0.7
Sorbitol	1.4
PEG-400	0.4
Propylene Glycol	0.3
Potassium Chloride	0.12
Sodium Chloride	0.1
Calcium Chloridc	0.0053
Magnisium Chloride	0.0064
Zinc Chloride	0.0015
AMP (95%)	0.57
Hydrochloric Acid	Adj. pH
Target pH	7.9
Purified Water	QS to 100%
Volume to make (L)	1

PET Results				
Lot Number	**PD Lot**	**03-34508**	**03-34433**	**03-34632**
P.aeruginosa (Day 7)	5.0	5.0	4.8	5.0
E.coli (Day 7)	5.0	5.0	4.9	5.0
P.aeruginosa (Day 14)	5.0	5.0	4.8	5.0
E.coli (Day 14)	5.0	5.0	4.9	5.0
P.aeruginosa (Day 28)	3.9*	3.9*	4.8	ND
E.coli (Day 28)	4.0*	4.0*	4.9	ND

*Rechallenge on day 14

**ND = Not Performed

Example 3

The formulations shown in Tables 4 and 5 below were prepared and tested in order to evaluate the effect of small variations in pH on the antimicrobial activity of the compositions.

Table 4
Effect of pH

	Formulation Number/Concentrations (w/v %)			
	FID 105784	**FID 105801**	**FID 105802**	**FID 105782**
Batch/Lot	**03-34662**	**03-34667**	**03-34669**	**03-34648**
Component				
HP-Guar	0.16	0.16	0.16	0.16
Boric Acid	0.7	0.7	0.7	0.7
Sorbitol	1.4	1.4	1.4	1.4
PEG-400	0.4	0.4	0.4	0.4
Propylene Glycol	0.3	0.3	0.3	0.3
Potassium Chloride	0.12	0.12	0.12	0.12
Sodium Chloride	0.1	0.1	0.1	0.1
Calcium Chloride	0.0053	0.0053	0.0053	0.0053
Magnisium Chloride	0.0064	0.0064	0.0064	0.0064
Zinc Chloride	0.00075	0.00075	0.00075	0.00075
AMP (95%)	0.6	0.6	0.6	0.6
Hydrochloric Acid	Adj. pH	Adj. pH	Adj. pH	Adj. pH
Target pH	7.0	7.3	7.6	7.9
Purified Water	QS to 100%	QS to 100%	QS to 100%	QS to 100%
Volume to make (L)	1	1	1	1
PET Results (Day 7)				
P.aeruginosa	-0.5	-0.6	-0.2	2.1
E.coli	-0.5	0.1	3.3	5.0

The results presented in Table 4 show that as the pH of the formula is increased, the activity against the test organisms consistently improved. At a pH of 7.9, the composition satisfied the USP 26 preservative efficacy requirements. However, the compositions having a pH of less than 7.9 did not have adequate antimicrobial activity to satisfy the USP requirements.

The antimicrobial activities of two formulations that were identical except for pH were also compared.. As shown in Table 5 below, the formulation having a pH of 7.7 did not satisfy USP 26 preservative efficacy requirements, but the formulation having a pH of 7.9 did meet those requirements.

Table 5

Effect of pH

Component	Concentration (w/v %)	Concentration (w/v %)
HP-Guar	0.16	0.16
Boric Acid	0.7	0.7
Sorbitol	1.4	1.4
PEG-400	0.4	0.4
Propylene Glycol	0.3	0.3
Potassium Chloride	0.12	0.12
Sodium Chloride	0.1	0.1
Calcium Chloride	0.0053	0.0053
Magnesium Chloride	0.0064	0.0064
Zinc Chloride	0.0015	0.0015
AMP (95%)	0.6	0.6
HCl/Adjust pH to	7.9	7.7
Purified Water	QS 100	QS 100
Microbiology	Passes USP	Fails USP

Example 4

The formulations shown in Table 6 below were prepared in order to evaluate the effect of zinc chloride on antimicrobial activity. The first two solutions, which contained no zinc and 1.5 ppm of zinc chloride, respectively, did not satisfy the USP 26 preservative efficacy requirements, but the third solution, which contained 15 ppm of zinc chloride, did meet those requirements.

Table 6
Effect of Zinc Level

	Formulation Number/Concentrations (w/v %)		
	FID 105689	**FID 104706**	**FID 105688**
Batch/Lot	**03-34434**	**03-34405**	**03-34433**
Component			
HP-Guar	0.16	0.16	0.16
Boric Acid	0.7	0.7	0.7
PEG-400	0.4	0.4	0.4
Propylene Glycol	0.3	0.3	0.3
Sorbitol	1.4	1.4	1.4
Sodium Chloride	0.1	0.1	0.1
Potassium Chloride	0.12	0.12	0.12
Calcium Chloride	0	0.0053	0.0053
Magnisium Chloride	0	0.0064	0.0064
Zinc Chloridc	0	0.00015	0.0015
AMP (95%)	0.6	0.6	0.6
Hydrochloric Acid	Adj. pH	Adj. pH	Adj. pH
Target pH	7.9	7.9	7.9
Purified Water	QS to 100%	QS to 100%	QS to 100%
PET Results (Day 7)			
P.aeruginosa	2.6	0.7	4.8
E.coli	0.9	1.8	4.9

Example 5

The effect of zinc chloride on antimicrobial activity was further investigated by evaluating the preservative efficacy of the solutions shown in Table 7 below. The zinc chloride concentrations evaluated were 1.5 ppm, 3.0 ppm, 3.5 ppm, 7.5 ppm and 15 ppm, respectively. The results presented at the bottom of Table 7 show greater antimicrobial activity with increasing concentrations of zinc chloride. At 15 ppm, the two test organisms were totally eliminated (i.e., no survivors).

Table 7
Effect of Zinc Levels

	Formulation Number/Concentration (w/v %)				
	FID 104706	**FID 105780**	**FID 105792**	**FID 105782**	**FID 105783**
Batch/Lot	**03-34628**	**03-34629**	**03-34652**	**03-34648**	**03-34632**
Component					
HP-Guar	0.16	0.16	0.16	0.16	0.16
Boric Acid	0.7	0.7	0.7	0.7	0.7
Sorbitol	1.4	1.4	1.4	1.4	1.4
PEG-400	0.4	0.4	0.4	0.4	0.4
Propylene Glycol	0.3	0.3	0.3	0.3	0.3
Potassium Chloride	0.12	0.12	0.12	0.12	0.12
Sodium Chloride	0.1	0.1	0.1	0.1	0.1
Calcium Chloride	0.0053	0.0053	0.0053	0.0053	0.0053
Magnisium Chloride	0.0064	0.0064	0.0064	0.0064	0.0064
Zinc Chloride	0.00015	0.0003	0.00045	0.00075	0.0015
AMP (95%)	0.6	0.6	0.6	0.6	0.6
Hydrochloric Acid	Adj. pH	Adj. pH	Adj. pH	Adj. pH	Adj. pH
Target pH	7.9	7.9	7.9	7.9	7.9
Purified Water	QS to 100%	QS to 100%	QS to 100%	QS to 100%	QS to 100%
PET Results (Day 7)					
P.aeruginosa	1.4	1.5	1.3	2.1	5.0
E.coli	1.0	2.1	3.9	5.0	5.0

5

Example 6

The role of amino alcohol concentration relative to antimicrobial activity was also investigated. The formulations shown in Table 8 below, which were identical except for the concentration of the amino alcohol AMP (95%), were utilized in this evaluation. As shown at the bottom of Table 8, the solutions containing AMP (95%) at concentrations of 0.2 and 0.4 w/v % did not satisfy the USP 26 preservative efficacy requirements against *Pseudomonas aeruginosa*, but the solution containing AMP (95%) at a concentration of 0.6 w/v % did meet those requirements.

Table 8
Amino Alcohol Concentration

	Formulation Number/Concentration (w/v %)		
	FID 105799	**FID 105800**	**FID 105782**
Batch/Lot	**03-34665**	**03-34666**	**03-34648**
Component	**Conc. (%)**	**Conc. (%)**	**Conc. (%)**
HP-Guar	0.16	0.16	0.16
Boric Acid	0.7	0.7	0.7
Sorbitol	1.4	1.4	1.4
PEG-400	0.4	0.4	0.4
Propylene Glycol	0.3	0.3	0.3
Potassium Chloride	0.12	0.12	0.12
Sodium Chloridc	0.1	0.1	0.1
Calcium Chloride	0.0053	0.0053	0.0053
Magnisium Chloride	0.0064	0.0064	0.0064
Zinc Chloride	0.00075	0.00075	0.00075
AMP (95%)	0.2	0.4	0.6
Hydrochloric Acid	Adj. pH	Adj. pH	Adj. pH
Target pH	7.9	7.9	7.9
Purified Water	QS to 100%	QS to 100%	QS to 100%
Volume to make (L)	1	1	1
PET Rcsults (Day 7)			
P.aeruginosa	-0.7	-0.2	2.1
E.coli	5.0	4.9	5.0

Example 7

The above-described preservative system was also evaluated relative to ophthalmic formulations containing the therapeutic agents travoprost and patanol, respectively. The results of show that these compositions are projected to satisfy preservative efficacy requirements.

Table 9

COMPONENT	% w/v	% w/v	% w/v	% w/v	% w/v	% w/v	% w/v
AL6221	0.004	0.004	0.004	0.004	0.004	0.004	0.004
Polyoxyl 40 HCO	0.5	0.5	0.5	0.5	0.5	0.5	0.75
Zinc Chloride	0.0025	0.0025	0.0025	0.0025	0.0025	0.0025	0.0025
Boric Acid	1	1	1	1	1	1	1
Sorbitol	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Propylene Glycol	0	0.25	0.5	0.75	0.75	0.75	0.25
NaOH/HCl q.s. pH	6.0	6.0	6.0	6.0	6.0	6.0	6.0
Purified Water q.s. 100%	100	100	100	100	100	100	100
Osmolality	176	214	248	272	282	282	214
6 Hr. and 24 Hr. Staph A.	-	-	-	-	-	0.0 & 0.1	-
6 and 24 Hr. Pseudomonas	-	-	-	-	-	1.2 & 2.3	-
6 Hr. and 24 Hr. E. Coli	-	-	-	-	-	1.0 & 1.5	-
7 Day Staph A.	2.6	4.9	4.9	5.0	4.4	4.9	4.9
7 Day Pseudomonas A.	4.6	5.0	5.0	4.0	5.1	5.1	5.0
7 Day E. Coli	2.7	2.7	2.3	3.2 [d]	2.6	2.7	3.0
7 Day Candida A.	0.1	0.0	0.2	0.2	0.2	0.2	0.0
7 Day A. Niger	2.2	2.6	2.6	1.8	2.8	2.3	2.9

Example 8

The results obtained with the formulations shown below demonstrate the role of zinc concentration.

Table 10

FID Number	**FID 105937**	**FID 105935**	**FID 105926**	**FID 105936**
Bacth/Lot	**03-34915**	**03-34913**	**03-34904**	**03-34914**
AL-12355 (HP-8A Guar)	0.16	0.16	0.16	0.16
Boric Acid	1.0	1.0	1.0	1.0
PEG-400	0.4	0.4	0.4	0.4
Propylene Glycol	0.3	0.3	0.3	0.3
Potassium Chloride	0.13	0.13	0.13	0.13
Calcium Chloride	0.0053	0.0053	0.0053	0.0053
Magnesium Chloride	0.0064	0.0064	0.0064	0.0064
Zinc Chloride	N/A	0.00075	0.0015	0.00225
Sodium Hydroxide	Adj. pH	Adj. pH	Adj. pH	Adj. pH
Tris	N/A	N/A	N/A	N/A
Hydrochloric Acid	Adj. pH	Adj. pH	Adj. pH	Adj. pH
Target pH	7.4	7.4	7.4	7.4
Purified Water	QS to 100%	QS to 100%	QS to 100%	QS to 100%
7 days P. aeruginosa	0.6	2.1	3.9	3.2
7 days E. coli	0.1	3.1	5.0	5.0
14 days P. aeruginosa	N/A	2.9	5.1	4.3
14 days E. coli	N/A	3.4	5.0	5.0
28 days P. aeruginosa	N/A	N/A	5.1	5.1
28 days E. coli	N/A	N/A	5.0	5.0

Example 9

The following formulations further illustrate the efficacy of preservative systems containing zinc and borate/polyol complexes.

Table 11

FID Number	FID 105973	FID 105974	FID 105975	FID 105976	FID 105977	FID 105978
Bacth/Lot	**03-34977**	**03-34978**	**03-34979**	**03-34980**	**03-34981**	**03-34982**
Boric Acid	1.0	1.0	1.0	1.0	1.0	1.0
Propylene Glycol	0.4	0.4	0.4	0.4	0.4	0.4
Zinc Chloride	0.0015	0.0015	0.0015	0.0015	0.0015	0.0015
Polyoxyl 40 Hydrogenated Castor Oil	0.5	0.05	0.5	0.5	0.5	0.5
Disodium EDTA	N/A	0.05	0.05	N/A	0.05	0.05
Polyquad	N/A	N/A	0.001	N/A	N/A	0.001
Tromethamine	Adj. pH	Adj. pH	Adj. pH	Adj. pH	Adj. pH	Adj. pH
Hydrochloric Acid	Adj. pH	Adj. pH	Adj. pH	Adj. pH	Adj. pH	Adj. pH
Target pH	6.0	6.0	6.0	6.0	6.0	6.0
Purified Water	QS to 100%	QS to 100%	QS to 100%	QS to 100%	QS to 100%	QS to 100%
7 days P. aeruginosa	5.1	5.1	5.1	5.1	5.1	5.1
7 days E. coli	3.3	1.6	4.9	3.9	0.6	4.9
14 days P. aeruginosa	5.1	5.1	5.1	5.1	NT	5.1
14 days E. coli	4.9	1.9	4.9	4.9	NT	4.9

NT=Not tested due to Day 7 Failure

ID Number	FID 105982	FID 105983	FID 105984	FID 105985	FID 105986
Bacth/Lot	**03-034988**	**03-034989**	**03-34990**	**03-34991**	**03-34992**
Boric Acid	1.0	1.0	1.0	1.0	1.0
Propylene Glycol	0.4	0.4	0.4	0.4	0.4
Zinc Chloride	0.0015	0.0015	0.0015	0.0015	0.0015
Polyoxyl 40 Stearate	0.1	0.1	0.1	0.1	0.1
Sodium Hydroxide	N/A	N/A	N/A	Adj. pH	Adj. pH
Hydrochloric Acid	Adj. pH	Adj. pH	Adj. pH	Adj. pH	Adj. pH
Target pH	7.4	7.55	7.7	7.4	7.55
Purified Water	QS to 100%	QS to 100%	QS to 100%	QS to 100%	QS to 100%
7 days P. aeruginosa	4.9	4.9	4.9	4.9	4.9
7 days E. coli	4.3	3.8	3.9	4.9	4.9
14 days P. aeruginosa	4.9	4.9	4.9	4.9	4.9
14 days E. coli	4.9	4.9	4.9	4.9	4.9

We Claim:

1. A multi-dose, self-preserved ophthalmic composition, said composition comprising an antimicrobial effective amount of a preservative system comprising 0.5 to 6.0 wt.% of a borate/polyol complex and zinc ions at a concentration of 0.000017 to 0.00017 moles per liter.

2. A composition according to Claim 1, wherein the zinc ions are provided in the form of zinc chloride at a concentration of from 0.0005 to 0.005 w/v %.

3. A composition according to Claim 1, wherein the composition is an aqueous ophthalmic solution having sufficient antimicrobial activity to satisfy USP preservative efficacy requirements.

4. A composition according to Claim 1, wherein the composition does not contain a conventional antimicrobial preservative.

5. A composition according to Claim 1, further comprising at least one therapeutically active agent.

6. A method of enhancing the antimicrobial activity of an aqueous ophthalmic pharmaceutical composition, which comprises including an antimicrobial effective amount of a preservative system comprising 0.5 to 6.0 wt.% of a borate/polyol complex and zinc ions at a concentration of 0.000017 to 0.00017 moles per liter.

7. A method according to Claim 6, wherein the zinc ions are provided in the form of zinc chloride at a concentration of from 0.0005 to 0.005 w/v %.

8. A method according to Claim 6, wherein the composition is a multi-dose, self-preserved ophthalmic solution having sufficient antimicrobial activity to satisfy USP preservative efficacy requirements.

9. A method according to Claim 8, wherein the composition does not contain a conventional antimicrobial agent.

10. A method according to Claim 6, wherein the composition contains a least one therapeutically active agent.

Abstract

The use of a borate/polyol and zinc system to enhance the antimicrobial activity of multi-dose pharmaceutical compositions is described. The compositions do not require a conventional anti-microbial preservative and therefore are referred to as being "self-preserved". The compositions possess sufficient antimicrobial activity to satisfy the preservative efficacy requirements of the USP for aqueous ophthalmic compositions.

Electronic Acknowledgement Receipt

EFS ID:	1226400
Application Number:	60827417
Confirmation Number:	9287
Title of Invention:	SELF-PRESERVED AQUEOUS PHARMACEUTICAL COMPOSITIONS
First Named Inventor:	Masood A. CHOWHAN
Customer Number:	26356
Filer:	Gregg C. Brown/Deborah Weinschenk
Filer Authorized By:	Gregg C. Brown
Attorney Docket Number:	2667Pr
Receipt Date:	28-SEP-2006
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Time Stamp:	21:42:56
Application Type:	Provisional
International Application Number:	

Payment information:

Submitted with Payment	yes
Payment was successfully received in RAM	$200
RAM confirmation Number	888
Deposit Account	010682
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Document Number	Document Description	File Name	File Size(Bytes)	Multi Part	Pages
1	Application Data Sheet	2667AppDataSheet.pdf	4152610	no	4
Warnings:					
Information:					
2		2667USPr.pdf	219954	yes	31

Multipart Description

Doc Desc	Start	End
Specification	1	28
Claims	29	30
Abstract	31	31

Warnings:					
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3	Fee Worksheet (PTO-875)	fee-info.pdf	8128	no	2
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Date of mailing
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International application No: PCT/US2007/079094

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 2677FWO	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/US2007/079094	International filing date *(day/month/year)* 20.09.2007	Priority date *(day/month/year)* 28.09.2006
International Patent Classification (IPC) or national classification and IPC INV. A61K9/00		
Applicant Alcon Research, Ltd.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 4 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
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      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
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4. This report contains indications relating to the following items:

- ☒ Box No. I Basis of the report
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
2008-07-25	11.12.2008
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Kardas-Llorens, Eyüp Telephone No. +49 89 2399-8652

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US2007/079094

Box No. I Basis of the report

1. With regard to the **language**, this report is based on

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3(a) and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4(a))
   - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-28 as originally filed

   Claims, Numbers

   1-10 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

5. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 70.2 (e)).

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-10
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-10
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-10
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Novelty:

A composition comprising a borate/polyol complex and zinc ions in the specified amounts as claimed in claim 1 is not disclosed in any one document cited in the search report.

The subject-matter of independent claims 1 and 6 is therefore new (Article 33(2) PCT).

Inventive Step:

The present problem to be solved by the present invention is to provide an ophthalmic composition with the desired antimicrobial activity to satisfy the preservation efficacy requirements.

This has been presently achieved by a composition comprising a borate/polyol complex and zinc ions as claimed which demonstrates the desired effects as demonstrated in present examples 4-6 in the claimed amounts of the actives.

From none of the cited prior art documents it was obvious to a person skilled in the art to combine a borate/polyol complex with a zinc compound to achieve the desired technical effects in the presently claimed concentrations.

The relevant prior art documents D1 (US2002/0123482), D2 (US2005/129771) and D3 (WO95/13050) comprise zinc below (D1 and D2) and above (D3) the minimum amount required in the ophthalmic composition which do not lead to the desired effects.

Thus, the solution to the problem proposed in claim 1 and 6 of the present application is considered as involving an inventive step (Article 33(3) PCT).

Re Item VIII

Certain observations on the international application

The wordings "having sufficient antimicrobial activity to satisfy USP preservative efficacy requirements" in claim 3 and 8 are not clear, since it is not clear how the "sufficient antimicrobial activity" and said "preservative efficacy requirements" have to be.

Also from the wording "conventional antimicrobial preservative" in claims 4 and 9 it is not clear which preservatives are meant.

PTO/SB/08a (06-09)
Approved for use through 06/30/2009. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	12441995
Filing Date	2009-03-19
First Named Inventor	Masood A. Chowhan
Art Unit	
Examiner Name	
Attorney Docket Number	2667 US F

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	4522806		1985-06-11	Muhlemann et al.	
	2	5221664		1993-06-22	Berkowitz et al.	
	3	5320843		1994-06-14	Raheja et al.	
	4	5352708		1994-10-04	Woodward et al.	
	5	5424078		1995-06-13	Dziabo et al.	
	6	5597559		1997-01-28	Olejnik et al.	
	7	5607698		1997-03-04	Martin et al.	
	8	5683993		1997-11-04	Tsao	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
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	Art Unit	
	Examiner Name	
	Attorney Docket Number	2667 US F

	9	5725887		1998-03-10	Martin et al.	
	10	5736165		1998-04-07	Ripley et al.	
	11	5741817		1998-04-21	Chowhan et al.	
	12	5817277		1998-10-06	Mowrey-McKee et al.	
	13	5858346		1999-01-12	Vehige et al.	
	14	5858996		1999-01-12	Tsao	
	15	6017861		2000-01-25	Fujiwara et al.	
	16	6024954		2000-02-15	Park et al.	
	17	6034043		2000-03-07	Fujiwara et al.	
	18	6121315		2000-09-19	Nair et al.	
	19	6143799		2000-11-07	Chowhan et al.	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
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	First Named Inventor	Masood A. Chowhan
	Art Unit	
	Examiner Name	
	Attorney Docket Number	2667 US F

	20	6319464		2001-11-20	Asgharian	
	21	6348190		2002-02-19	Illes et al.	
	22	6482799		2002-11-19	Tuse et al.	
	23	6492361		2002-12-10	Muller et al.	
	24	6503497		2003-01-07	Chowhan et al.	
	25	6583124		2003-06-24	Asgharian	

If you wish to add additional U.S. Patent citation information please click the Add button. Add

U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20020122831		2002-09-05	Mowrey-McKee et al.	
	2	20020123482		2002-09-05	Chowhan et al.	
	3	20050129771		2005-06-16	Asgharian	

If you wish to add additional U.S. Published Application citation information please click the Add button. Add

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	12441995
	Filing Date	2009-03-19
	First Named Inventor	Masood A. Chowhan
	Art Unit	
	Examiner Name	
	Attorney Docket Number	2667 US F

FOREIGN PATENT DOCUMENTS								Remove
Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] ¡	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	2003-104870	JP		2003-04-09	Rohto Pharmaceutical Co., Ltd. / Kiyobashi		☒
	2	95/13050	WO		1995-05-18	Ciba-Geigy AG		☐
	3	2005/097067	WO		2005-10-20	Bausch & Lomb Incorporated		☐
	4	2008/042619	WO		2008-04-10	Alcon Manufacturing, Ltd.		☐

If you wish to add additional Foreign Patent Document citation information please click the Add button Add

NON-PATENT LITERATURE DOCUMENTS			Remove
Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	Kabara, et al., Preservative-Free and Self-Preserving Cosmetics and Drugs – Principles and Practice, Chapter 1, pages 1-14, Marcel Dekker, Inc., 1997	☐
	2	McCarthy, "Metal Ions and Microbial Inhibitors", Cosmetic & Toiletries, 100:69-72, 1985	☐
	3	McCarthy, et al., "The Effect of Zinc Ions on the Antimicrobial Activity of Selected Preservatives", Journal of Pharmacy and Pharmacology, Vol. 41 (1989)	☐
	4	PCT International Preliminary Report On Patentability for corresponding application PCT/US2007/079094 with mailing date December 11, 2008	☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	12441995
	Filing Date	2009-03-19
	First Named Inventor	Masood A. Chowhan
	Art Unit	
	Examiner Name	
	Attorney Docket Number	2667 US F

	5	PCT International Search Report for corresponding application PCT/US2007/079094 with mailing date April 2, 2008	☐
	6	PCT Written Opinion for corresponding application PCT/US2007/079094 with mailing date April 2, 2008	☐
	7	Zeelie, et al., "Effects of Copper and Zinc Ions on the Germicidal Properties of Two Popular Pharmaceutical Antiseptic Agents, Cetylpyridinium Chloride and Povidone-iodine", Analyst, 123:503-507 (March 1998)	☐
	8	Zeelie, et al., "The Effects of Selected Metal Salts on the Microbial Activities of Agents used in the Pharmaceutical and Related Industries", Metal Compounds in Environment and Life, 4:193-200 (1992)	☐

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	12441995
	Filing Date	2009-03-19
	First Named Inventor	Masood A. Chowhan
	Art Unit	
	Examiner Name	
	Attorney Docket Number	2667 US F

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☒ See attached certification statement.

☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ None

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Scott A. Chapple, Reg. No. 46,287/	Date (YYYY-MM-DD)	2009-06-18
Name/Print	Scott A. Chapple	Registration Number	46,287

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 2677FWO	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/US2007/079094	International filing date *(day/month/year)* 20.09.2007	Priority date *(day/month/year)* 28.09.2006
International Patent Classification (IPC) or national classification and IPC INV. A61K9/00		
Applicant Alcon Research, Ltd.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 4 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
2008-07-25	11.12.2008
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Kardas-Llorens, Eyüp Telephone No. +49 89 2399-8652

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US2007/079094

Box No. I Basis of the report

1. With regard to the **language**, this report is based on

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3(a) and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4(a))
   - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-28 as originally filed

   Claims, Numbers

   1-10 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

5. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 70.2 (e)).

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-10
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-10
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-10
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Novelty:

A composition comprising a borate/polyol complex and zinc ions in the specified amounts as claimed in claim 1 is not disclosed in any one document cited in the search report.

The subject-matter of independent claims 1 and 6 is therefore new (Article 33(2) PCT).

Inventive Step:

The present problem to be solved by the present invention is to provide an ophthalmic composition with the desired antimicrobial activity to satisfy the preservation efficacy requirements.

This has been presently achieved by a composition comprising a borate/polyol complex and zinc ions as claimed which demonstrates the desired effects as demonstrated in present examples 4-6 in the claimed amounts of the actives.

From none of the cited prior art documents it was obvious to a person skilled in the art to combine a borate/polyol complex with a zinc compound to achieve the desired technical effects in the presently claimed concentrations.

The relevant prior art documents D1 (US2002/0123482), D2 (US2005/129771) and D3 (WO95/13050) comprise zinc below (D1 and D2) and above (D3) the minimum amount required in the ophthalmic composition which do not lead to the desired effects.

Thus, the solution to the problem proposed in claim 1 and 6 of the present application is considered as involving an inventive step (Article 33(3) PCT).

Re Item VIII

Certain observations on the international application

The wordings "having sufficient antimicrobial activity to satisfy USP preservative efficacy requirements" in claim 3 and 8 are not clear, since it is not clear how the "sufficient antimicrobial activity" and said "preservative efficacy requirements" have to be.

Also from the wording "conventional antimicrobial preservative" in claims 4 and 9 it is not clear which preservatives are meant.

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

To:
ALCON RESEARCH, LTD.
Attn. Brown, Gregg C.
6201 South Freeway
TB 4-8
Fort Worth TX 76134-2099
ETATS-UNIS D'AMERIQUE

Applicant's or agent's file reference ~~2677F~~WO	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/US2007/079094	International filing date *(day/month/year)* 20/09/2007
Applicant ALCON MANUFACTURING, LTD.	

Date of mailing *(day/month/year)* 02/04/2008

1. [x] The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the International Search Report.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Fascimile No.: (41-22) 338.82.70

   For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   [ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

   [ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

   See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Georg Hutterer

Form PCT/ISA/220 (October 2005)

(See notes on accompanying sheet)

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report and the written opinion of the International Searching Authority, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims,description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only (see *PCT Applicant's Guide*, Volume I/A, Annexes B1 and B2).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, Volume I/A, paragraph 296).

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
2677FWO		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US2007/079094	20/09/2007	28/09/2006
Applicant		
ALCON MANUFACTURING, LTD.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language,** the international search was carried out on the basis of:
      [X] the international application in the language in which it was filed
      [ ] a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. [ ] This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [ ] **Certain claims were found unsearchable** (See Box No. II)

3. [ ] **Unity of invention is lacking** (see Box No III)

4. With regard to the **title,**
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings,**
   a. the figure of the **drawings** to be published with the abstract is Figure No. _____
      [ ] as suggested by the applicant
      [ ] as selected by this Authority, because the applicant failed to suggest a figure
      [ ] as selected by this Authority, because this figure better characterizes the invention
   b. [ ] none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/079094

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/00 A61K31/00 A61K47/02 A61K47/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2002/123482 A1 (CHOWHAN MASOOD A [US] ET AL) 5 September 2002 (2002-09-05) paragraphs [0013], [0016], [0019], [0021] - [0024]; claims 1,15,16	1-10
X	US 2005/129771 A1 (ASGHARIAN BAHRAM [US]) 16 June 2005 (2005-06-16) paragraphs [0016] - [0019], [0024], [0027], [0030], [0032]; example 2	1-10
X	WO 95/13050 A (CIBA GEIGY AG [CH]; OLEJNIK OREST [US]; WENDEL FRED W [US]) 18 May 1995 (1995-05-18) page 2, line 8 - page 4, line 5; claims 1-25	1-10

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 March 2008	02/04/2008

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Rauter, Anton

2

Form PCT/ISA/210 (second sheet) (April 2005)

ternational application No
PCT/US2007/079094

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 6 143 799 A (CHOWHAN MASOOD [US] ET AL) 7 November 2000 (2000-11-07) claims 1-21	1-10
Y	WO 2005/097067 A (BAUSCH & LOMB [US]; XIA ERNING [US]; SALAMONE JOSEPH C [US]; BORAZJANI) 20 October 2005 (2005-10-20) claims 1-78	1-10

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2007/079094

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2002123482 A1	05-09-2002	NONE	
US 2005129771 A1	16-06-2005	NONE	
WO 9513050 A	18-05-1995	AU 8060394 A	29-05-1995
		CA 2173255 A1	18-05-1995
		US 5597559 A	28-01-1997
		ZA 9408961 A	13-07-1995
US 6143799 A	07-11-2000	NONE	
WO 2005097067 A	20-10-2005	AU 2005231147 A1	20-10-2005
		BR PI0509363 A	11-09-2007
		CA 2560724 A1	20-10-2005
		CN 1938003 A	28-03-2007
		EP 1734923 A1	27-12-2006
		JP 2007530685 T	01-11-2007
		KR 20060135006 A	28-12-2006
		US 2005214382 A1	29-09-2005

ATENT COOPERATION TR[illegible].TY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2007/079094	20.09.2007	28.09.2006

International Patent Classification (IPC) or both national classification and IPC
INV. A61K9/00 A61K31/00 A61K47/02 A61K47/10

Applicant
ALCON MANUFACTURING, LTD.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Rauter, Anton Telephone No. +49 89 2399-8645

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☐ on paper

      ☐ in electronic form

   c. time of filing/furnishing:

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in electronic form.

      ☐ furnished subsequently to this Authority for the purposes of search.

4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-10
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-10
Industrial applicability (IA)	Yes:	Claims	1-10
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item V.

1 Reference is made to the following documents:

D1 : US 2002/123482 A1 (CHOWHAN MASOOD A [US] ET AL) 5 September 2002 (2002-09-05)

D2 : US 2005/129771 A1 (ASGHARIAN BAHRAM [US]) 16 June 2005 (2005-06-16)

D3 : WO 95/13050 A (CIBA GEIGY AG [CH]; OLEJNIK OREST [US]; WENDEL FRED W [US]) 18 May 1995 (1995-05-18)

D4 : US 6 143 799 A (CHOWHAN MASOOD [US] ET AL) 7 November 2000 (2000-11-07)

D5 : WO 2005/097067 A (BAUSCH &; LOMB [US]; XIA ERNING [US]; SALAMONE JOSEPH C [US]; BORAZJANI) 20 October 2005 (2005-10-20)

2 INDEPENDENT CLAIMS 1 AND 6

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1 and 6 is not new in the sense of Article 33(2) PCT.

The claimed product, *ie* the ophthalmic composition comprises

- a borate/polyol complex in a certain amount,
and
- zinc ions in a certain amount.

Document D1 discloses *eg* in claim 16 such product (see also [0013]). The disclosure of D1, furthermore, clearly expresses that the essential components of the product represent an antimicrobial preservative system (see *eg* the abstract), thus present claim 6, likewise lacks novelty.

Further novelty destroying disclosure can be taken from D2 and D3.

3 DEPENDENT CLAIMS 2-5 and 7-10

The said dependent claims do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty (Article 33(2) PCT). The citations D1 - D3 do disclose the embodiments where, *eg* no further antimicrobial is present, or that an active agent is present (see *eg* the indications given in the search report).

Electronic Acknowledgement Receipt

EFS ID:	5539918
Application Number:	12441995
International Application Number:	
Confirmation Number:	7046
Title of Invention:	SELF-PRESERVED AQUEOUS PHARMACEUTICAL COMPOSITIONS
First Named Inventor/Applicant Name:	Masood A. Chowhan
Customer Number:	26356
Filer:	Scott Chapple/Barbara McKenzie
Filer Authorized By:	Scott Chapple
Attorney Docket Number:	2667 US F
Receipt Date:	18-JUN-2009
Filing Date:	
Time Stamp:	11:13:34
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	2667_US_F_IDS_061809.pdf	53728 2c52956b7221b006894ac49795c030e9ddf4e9d2	no	2

Warnings:	
Information:	

2	Information Disclosure Statement (IDS) Filed (SB/08)	2667_US_F_IDS_SB08a_061809.pdf	1121031 da5d7085efc4089d72751f3282f7f52b7c2a9d06	no	7
Warnings:					
Information:					
3	Foreign Reference	JP_2003_104870_A.pdf	689401 9d9d6f5a2b26b618c33a6ab071ddbf0ebe1bd3e7	no	17
Warnings:					
Information:					
4	Foreign Reference	JP_2003_104870_translation.pdf	1391316 418fa6896ad45d910e4d35dbf13e1f0161dd5faf	no	40
Warnings:					
Information:					
5	Foreign Reference	WO_95_013050_A1.pdf	899311 77c892e079609eebc8c2e887964379226245f36d	no	23
Warnings:					
Information:					
6	Foreign Reference	WO_2005_097067_A1.pdf	1851911 09ef491e2103f61292d1affcd377fedf0070e7f0	no	36
Warnings:					
Information:					
7	Foreign Reference	WO_2008_042619_A2.pdf	1230684 16ffa5658f3d6c93e53275b8b9cbfb5ed6c224fc	no	31
Warnings:					
Information:					
8	NPL Documents	Kabara_et_al_1997_PreservativeFree_1-14.pdf	1119845 3806fb2237c7f67baf64bd21637384604ba0b8f3	no	24
Warnings:					
Information:					
9	NPL Documents	McCarthy_et_al_1985_CT_100_69-72.pdf	408963 f0bd918bda22e2284bb396b48e2ef8d97f0b6fbf	no	4
Warnings:					
Information:					
10	NPL Documents	McCarthy_et_al_1989_JPP_41_114P.pdf	168868 b1d4b63da1341c0964b83ebf5acaabb15f5b78dd	no	1
Warnings:					
Information:					

11	NPL Documents	PCT-2007-079094_IPER.pdf	167772 bcc6cb9a9a94b0990fd0954ecc14b249cb94caf6	no	4
Warnings:					
Information:					
12	NPL Documents	PCT-2007-079094_SearchRpt.pdf	286618 108d2c583fd5c6feaea7e3e13b98f55ab46b6a01	no	6
Warnings:					
Information:					
13	NPL Documents	PCT-2007-079094_WrittenOp.pdf	157456 08b4f0ea1b194c126196d3175f3615e00fabda7a	no	5
Warnings:					
Information:					
14	NPL Documents	Zeelie_et_al_1998_Analyst_123_503-507.pdf	405364 bc6f5ccea4c9ac7a998b12546f81d9365de7b950	no	5
Warnings:					
Information:					
15	NPL Documents	Zeelie_et_al_1992_MCEL_4_193-200.pdf	567484 77004f2c72d772bbffe3db7fd7f7a82c36b43ed3	no	8
Warnings:					
Information:					
		Total Files Size (in bytes):	10519752		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

<u>New Applications Under 35 U.S.C. 111</u>
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

<u>National Stage of an International Application under 35 U.S.C. 371</u>
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

<u>New International Application Filed with the USPTO as a Receiving Office</u>
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Masood A. Chowhan et al.

U.S. Serial No. 12/441,995

Confirmation No.: 7046

Filed: March 19, 2009

Examiner:

Group Art Unit:

CERTIFICATE OF FILING VIA EFS-WEB

I hereby certify that this correspondence is being submitted to the Mail Stop Amendment; Commissioner for Patents, P.O. Box 1450, Alexandria, VA. 22313-1450 via EFS-Web on this date:

June 18, 2009.

By: /Barbara McKenzie/
Barbara McKenzie

For: SELF PRESERVED AQUEOUS PHARMACEUTICAL COMPOSITIONS

INFORMATION DISCLOSURE STATEMENT PURSUANT TO 37 C.F.R. 1.56, 1.97(b)(3), AND 1.98

Mail Stop Amendment
Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In accordance with Rules 56, 97 and 98 of the Rules of Practice in Patent Cases (37 C.F.R. § 1.56, 1.97(b)(3) and 1.98), enclosed is Form PTO/SB/08a Information Disclosure Statement by Applicant.

Because the PTO has waived the requirement under 37 CFR 1.98(a)(2) to submit copies of each cited U.S. patent and patent application publication in all U.S. national patent applications filed after June 30, 2003, none are enclosed. Only copies of cited foreign patent documents and non-patent literature are enclosed. Applicants do not concede that these materials constitute prior art within the meaning of the United States patent statutes.

Applicants requests that the listed references be considered during prosecution of this application and that the references appear among the "References Cited" on any patent issuing from the application.

This statement is filed before the mailing of a first Office Action on the merits pursuant to 37 C.F.R. § 1.97(b), and therefore no fee for the consideration of this statement is enclosed herewith. However, the Commissioner is hereby authorized to charge any amount required for the consideration of this statement to Deposit Account No. 010682 of Alcon Research, Ltd.

Respectfully submitted,

18 June 2009
Date

Scott A. Chapple
Registration No. 46,287

Address for Correspondence:
Alcon Research, Ltd.
Attn: Scott A. Chapple
6201 S. Freeway, TB4-8
Fort Worth, TX 76134-2099
Phone: 817-615-5288

Attorney Docket: 2667 US F

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Masood A. Chowhan et al.

U.S. Serial No. 12/441,995

Confirmation No.: 7046

Filed: March 19, 2009

Examiner:

Group Art Unit:

CERTIFICATE OF FILING VIA EFS-WEB

I hereby certify that this correspondence is being submitted to the Mail Stop Amendment; Commissioner for Patents, P.O. Box 1450, Alexandria, VA. 22313-1450 via EFS-Web on this date:

October 8, 2009.

By: /Barbara McKenzie/
Barbara McKenzie

For: SELF PRESERVED AQUEOUS PHARMACEUTICAL COMPOSITIONS

SECOND PRELIMINARY AMENDMENT

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Please enter the following amendments prior to formal examination of the above-identified application.

Amendment to the Specification begin on page 2 of this paper.

Amendments to the Claims are reflected in the listing of claims that begins on page 3 of this paper.

Remarks begin on page 5 of this paper.

AMENDMENT TO THE SPECIFICATION

Please amend the paragraph starting at page 13, line 11 as follows:

The ophthalmic compositions of the present invention may be formulated to include one or more agents to enhance ocular comfort and/or retention of the compositions on the eye following topical application. The types of agents which may be utilized include: cellulose derivatives, such as hydroxypropyl methylcellulose ("HPMC"); Dextran 70; polyethylene glycol; propylene glycol; carboxy vinyl polymers; polyvinyl alcohol polymers or copolymers; and polysaccharides. The preferred polysaccharides are hydroxypropyl guar and other galactomannan polymers described in U.S. Patent No. 6,583,124~~6,583,125~~ (Asgharian). The entire contents of the '124~~'125~~ patent are hereby incorporated in the present specification by reference.

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions and listings of claims in the application:

1. (currently amended) A multi-dose, self-preserved ophthalmic composition, said composition comprising an antimicrobial effective amount of a preservative system comprising 0.5 to 6.0 wt. % of a borate/polyol complex and zinc ions provided in the form of zinc chloride at a concentration of from 0.0005 to 0.005 w/v % ~~zinc ions at a concentration of 0.000017 to 0.00017 moles per liter~~.

2. (canceled)

3. (original) A composition according to Claim 1, wherein the composition is an aqueous ophthalmic solution having sufficient antimicrobial activity to satisfy USP preservative efficacy requirements.

4. (original) A composition according to Claim 1, wherein the composition does not contain a conventional antimicrobial preservative.

5. (original) A composition according to Claim 1, further comprising at least one therapeutically active agent.

6. (currently amended) A method of enhancing the antimicrobial activity of an aqueous ophthalmic pharmaceutical composition, which comprises including an antimicrobial effective amount of a preservative system comprising 0.5 to 6.0 wt.% of a borate/polyol complex and zinc ions provided in the form of zinc chloride at a concentration of from 0.0005 to 0.005 w/v % ~~zinc ions at a concentration of 0.000017 to 0.00017 moles per liter~~.

7. (canceled)

8. (original) A method according to Claim 6, wherein the composition is a multidose, self preserved ophthalmic solution having sufficient antimicrobial activity to satisfy USP preservative efficacy requirements.

9. (original) A method according to Claim 8, wherein the composition does not contain a conventional antimicrobial agent.

10. (original) A method according to Claim 6, wherein the composition contains a least one therapeutically active agent.

REMARKS

Claims 3-5 are original, claims 2 and 7 are canceled and claims 1, 6, 8-10 are amended.

Applicants respectfully request consideration of the pending claims and believes no fee is due with this response. However, the Commissioner is authorized to charge any fees which may be required or to credit any overpayment to Deposit Account No. 010682 in the name of Alcon Laboratories, Inc.

Respectfully submitted,

ALCON RESEARCH, LTD.

October 8, 2009
Date

Scott A. Chapple, Agent
Reg. No. 46,287

Address for Correspondence:
Scott A. Chapple
Alcon Research, Ltd.
6201 S. Freeway, Mail Code TB4-8
Fort Worth, TX 76134-2099
Phone: 817-615-5288

Attorney Docket: 2667 US F

Electronic Acknowledgement Receipt

EFS ID:	6227433
Application Number:	12441995
International Application Number:	
Confirmation Number:	7046
Title of Invention:	SELF-PRESERVED AQUEOUS PHARMACEUTICAL COMPOSITIONS
First Named Inventor/Applicant Name:	Masood A. Chowhan
Customer Number:	26356
Filer:	Scott Chapple/Barbara McKenzie
Filer Authorized By:	Scott Chapple
Attorney Docket Number:	2667 US F
Receipt Date:	08-OCT-2009
Filing Date:	
Time Stamp:	14:52:42
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		2667_US_F_PrelimAmend2_100809.pdf	109624 f28fd958ab850b8ef9776391d44ff8b8de8b7287	yes	5

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Preliminary Amendment	1	1
	Specification	2	2
	Claims	3	4
	Applicant Arguments/Remarks Made in an Amendment	5	5
Warnings:			
Information:			
	Total Files Size (in bytes):	109624	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PATENT APPLICATION FEE DETERMINATION RECORD
Effective October 02, 2008

Application or Docket Number: 12144195

CLAIMS AS FILED - PART I

	(Column 1)	(Column 2)
U.S. NATIONAL STAGE FEES		
BASIC FEE	SMALL ENT. = $ 150	LARGE ENT. = $ 300
EXAMINATION FEE	Satisfies PCT Article 33(1)-(4) = $ 50 / $ 100	All other situations = $ 110 / $ 220
SEARCH FEE	U.S. is ISA = $ 50 / $ 100 ALL other countries = $ 200 / $ 400	ALL other situations = $ 270 / $ 540
FEE FOR EXTRA SPEC. PGS.	minus 100 =	/ 50 =
TOTAL CHARGEABLE CLAIMS	8 minus 20 =	*
INDEPENDENT CLAIMS	2 minus 3 =	*
MULTIPLE DEPENDENT CLAIM PRESENT		

* If the difference in column 1 is less than zero, enter "0" in column 2

SMALL ENTITY TYPE ☐	RATE	FEE	OR	OTHER THAN SMALL ENTITY	RATE	FEE
	BASIC FEE	$165	OR		BASIC FEE	$330
	EXAM. FEE	$110			EXAM. FEE	$220
	SEARCH FEE	$215			SEARCH FEE	$430
	X $ 135 =				X $ 270 =	
	X $ 26 =		OR		X $ 52 =	
	X $ 110 =		OR		X $ 220 =	
	+ $ 195 =		OR		+ $ 390 =	
	TOTAL		OR		TOTAL	430

CLAIMS AS AMENDED - PART II

AMENDMENT A

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM ☐				

SMALL ENTITY	RATE	ADDITIONAL FEE	OR	OTHER THAN SMALL ENTITY	RATE	ADDITIONAL FEE
	X $ 26 =		OR		X $ 52 =	
	X $ 110 =		OR		X $ 220 =	
	+ $ 195 =		OR		+ $ 390 =	
	TOTAL ADDIT. FEE		OR		TOTAL ADDIT. FEE	

AMENDMENT B

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM ☐				

	RATE	ADDITIONAL FEE	OR	RATE	ADDITIONAL FEE
	X $ 26 =		OR	X $ 52 =	
	X $ 110 =		OR	X $ 220 =	
	+ $ 195 =		OR	+ $ 390 =	
	TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than '20', enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than '3', enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

MULTIPLE DEPENDENT CLAIM CALCULATION SHEET

(FOR USE WITH FORM PTO-875)

SERIAL NO.	FILING DATE
12/44/1995	

CLAIMS

	AS FILED		AFTER 1st AMENDMENT		AFTER 2nd AMENDMENT	
	IND.	DEP.	IND.	DEP.	IND.	DEP.
1						
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50						
TOTAL IND.			2			
TOTAL DEP.			4			
TOTAL CLAIMS			6			

	AS FILED		AFTER 1st AMENDMENT		AFTER 2nd AMENDMENT	
	IND.	DEP.	IND.	DEP.	IND.	DEP.
51						
52						
53						
54						
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UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

U.S. APPLICATION NUMBER NO.	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
12/441,995	Masood A. Chowhan	2667 US F

26356
ALCON
IP LEGAL, TB4-8
6201 SOUTH FREEWAY
FORT WORTH, TX 76134

INTERNATIONAL APPLICATION NO.	
PCT/US07/79094	
I.A. FILING DATE	PRIORITY DATE
09/20/2007	09/28/2006

CONFIRMATION NO. 7046
371 ACCEPTANCE LETTER

OC000000038343623

Date Mailed: 10/20/2009

NOTICE OF ACCEPTANCE OF APPLICATION UNDER 35 U.S.C 371 AND 37 CFR 1.495

The applicant is hereby advised that the United States Patent and Trademark Office in its capacity as a Designated / Elected Office (37 CFR 1.495), has determined that the above identified international application has met the requirements of 35 U.S.C. 371, and is ACCEPTED for national patentability examination in the United States Patent and Trademark Office.

The United States Application Number assigned to the application is shown above and the relevant dates are:

03/19/2009	03/28/2009
DATE OF RECEIPT OF 35 U.S.C. 371(c)(1), (c)(2) and (c)(4) REQUIREMENTS	DATE OF COMPLETION OF ALL 35 U.S.C. 371 REQUIREMENTS

A Filing Receipt (PTO-103X) will be issued for the present application in due course. **THE DATE APPEARING ON THE FILING RECEIPT AS THE " FILING DATE" IS THE DATE ON WHICH THE LAST OF THE 35 U.S.C. 371 (c)(1), (c)(2) and (c)(4) REQUIREMENTS HAS BEEN RECEIVED IN THE OFFICE. THIS DATE IS SHOWN ABOVE.** *The filing date of the above identified application is the international filing date of the international application (Article 11(3) and 35 U.S.C. 363).* Once the Filing Receipt has been received, send all correspondence to the Group Art Unit designated thereon.

The following items have been received:

- Copy of the International Application filed on 03/19/2009
- Copy of the International Search Report filed on 03/19/2009
- Copy of IPE Report filed on 03/19/2009
- Preliminary Amendments filed on 03/19/2009
- Information Disclosure Statements filed on 06/18/2009
- Oath or Declaration filed on 03/19/2009
- U.S. Basic National Fees filed on 03/19/2009
- Priority Documents filed on 03/19/2009

Applicant is reminded that any communications to the United States Patent and Trademark Office must be mailed to the address given in the heading and include the U.S. application no. shown above (37 CFR 1.5)

CHARITTA A SHELTON

Telephone: (703) 756-1471

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
12/441,995	03/19/2009		980	2667 US F	8	2

CONFIRMATION NO. 7046

26356
ALCON
IP LEGAL, TB4-8
6201 SOUTH FREEWAY
FORT WORTH, TX 76134

FILING RECEIPT

OC000000038343622

Date Mailed: 10/20/2009

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Applicant(s)

Masood A. Chowhan, Arlington, TX;
David J. Keith, Washington, MO;

Power of Attorney: The patent practitioners associated with Customer Number 26356

Domestic Priority data as claimed by applicant

This application is a 371 of PCT/US07/79094 09/20/2007
which claims benefit of 60/827,417 09/28/2006

Foreign Applications

If Required, Foreign Filing License Granted: 10/15/2009

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 12/441,995**

Projected Publication Date: 01/28/2010

Non-Publication Request: No

Early Publication Request: No

Title

SELF PRESERVED AQUEOUS PHARMACEUTICAL COMPOSITIONS

Preliminary Class

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4158).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier

license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

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United States Patent and Trademark Office
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www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
12/441,995	03/19/2009	Masood A. Chowhan	2667 US F

CONFIRMATION NO. 7046

PUBLICATION NOTICE

26356
ALCON
IP LEGAL, TB4-8
6201 SOUTH FREEWAY
FORT WORTH, TX 76134

OC00000039901740

Title:SELF PRESERVED AQUEOUS PHARMACEUTICAL COMPOSITIONS

Publication No.US-2010-0021562-A1
Publication Date:01/28/2010

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Office of Public Records. The Office of Public Records can be reached by telephone at (703) 308-9726 or (800) 972-6382, by facsimile at (703) 305-8759, by mail addressed to the United States Patent and Trademark Office, Office of Public Records, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently http://pair.uspto.gov/. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/441,995	03/19/2009	Masood A. Chowhan	2667 US F	7046

26356 7590 06/24/2010

ALCON
IP LEGAL, TB4-8
6201 SOUTH FREEWAY
FORT WORTH, TX 76134

EXAMINER	
FAY, ZOHREH A	

ART UNIT	PAPER NUMBER
1612	

MAIL DATE	DELIVERY MODE
06/24/2010	PAPER

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.

Office Action Summary	Application No.	Applicant(s)	
	12/441,995	CHOWHAN ET AL.	
	Examiner	Art Unit	
	ZOHREH A. FAY	1612	

-- 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 _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ 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

4)☒ Claim(s) *1-6 and 8-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 8-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ 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).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

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).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ 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) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/18/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-6 and 8-10 are presented for examination.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-6 and 8-10 are rejected under 35 U.S.C. 102(b) as being anticipated by Chowhan et al. (2002/0123482).

Chowhan et al. teach a multidose self preserved ophthalmic composition comprising 0.5 to 6% borax/polyol complex and zinc ion in the form of Zinc chloride at the claimed range concentration in combination with an active ingredient, such as amino acids. See Para [0013], Para [0020], Para [0021] and claims 15-16. The above reference makes clear that the claimed composition and method of use id old and well known.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ZOHREH A. FAY whose telephone number is (571)272-0573. The examiner can normally be reached on Monday to Friday 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Fredrick Krass can be reached on (571) 272-0580. 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). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

ZF
/Zohreh A Fay/
Primary Examiner, Art Unit 1612

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12441995	CHOWHAN ET AL.
	Examiner	**Art Unit**
	ZOHREH A FAY	1612

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	06/21/2010								
	1	✓								
	2	✓								
	3	✓								
	4	✓								
	5	✓								
	6	✓								
	7	-								
	8	✓								
	9	✓								
	10	✓								

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12441995	CHOWHAN ET AL.
	Examiner	Art Unit
	ZOHREH A FAY	1612

SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
West	6/19/2010	ZF
Inventor search	6/19/2010	ZF

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner

PTO/SB/08a (06-09)
Approved for use through 06/30/2009. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	12441995
Filing Date	2009-03-19
First Named Inventor	Masood A. Chowhan
Art Unit	
Examiner Name	
Attorney Docket Number	2667 US F

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
/ZF/	1	4522806		1985-06-11	Muhlemann et al.	
	2	5221664		1993-06-22	Berkowitz et al.	
	3	5320843		1994-06-14	Raheja et al.	
	4	5352708		1994-10-04	Woodward et al.	
	5	5424078		1995-06-13	Dziabo et al.	
	6	5597559		1997-01-28	Olejnik et al.	
	7	5607698		1997-03-04	Martin et al.	
	8	5683993		1997-11-04	Tsao	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	12441995
	Filing Date	2009-03-19
	First Named Inventor	Masood A. Chowhan
	Art Unit	
	Examiner Name	
	Attorney Docket Number	2667 US F

/ZF/	9	5725887		1998-03-10	Martin et al.	
	10	5736165		1998-04-07	Ripley et al.	
	11	5741817		1998-04-21	Chowhan et al.	
	12	5817277		1998-10-06	Mowrey-McKee et al.	
	13	5858346		1999-01-12	Vehige et al.	
	14	5858996		1999-01-12	Tsao	
	15	6017861		2000-01-25	Fujiwara et al.	
	16	6024954		2000-02-15	Park et al.	
	17	6034043		2000-03-07	Fujiwara et al.	
	18	6121315		2000-09-19	Nair et al.	
	19	6143799		2000-11-07	Chowhan et al.	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	12441995
	Filing Date	2009-03-19
	First Named Inventor	Masood A. Chowhan
	Art Unit	
	Examiner Name	
	Attorney Docket Number	2667 US F

/ZF/	20	6319464		2001-11-20	Asgharian	
	21	6348190		2002-02-19	Illes et al.	
	22	6482799		2002-11-19	Tuse et al.	
	23	6492361		2002-12-10	Muller et al.	
	24	6503497		2003-01-07	Chowhan et al.	
	25	6583124		2003-06-24	Asgharian	

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U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
/ZF/	1	20020122831		2002-09-05	Mowrey-McKee et al.	
/ZF/	2	20020123482		2002-09-05	Chowhan et al.	
/ZF/	3	20050129771		2005-06-16	Asgharian	

If you wish to add additional U.S. Published Application citation information please click the Add button. Add

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	12441995
Filing Date	2009-03-19
First Named Inventor	Masood A. Chowhan
Art Unit	
Examiner Name	
Attorney Docket Number	2667 US F

FOREIGN PATENT DOCUMENTS Remove

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
/ZF/	1	2003-104870	JP		2003-04-09	Rohto Pharmaceutical Co., Ltd. / Kiyobashi		☒
/ZF/	2	95/13050	WO		1995-05-18	Ciba-Geigy AG		☐
/ZF/	3	2005/097067	WO		2005-10-20	Bausch & Lomb Incorporated		☐
/ZF/	4	2008/042619	WO		2008-04-10	Alcon Manufacturing, Ltd.		☐

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Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
/ZF/	1	Kabara, et al., Preservative-Free and Self-Preserving Cosmetics and Drugs – Principles and Practice, Chapter 1, pages 1-14, Marcel Dekker, Inc., 1997	☐
/ZF/	2	McCarthy, "Metal Ions and Microbial Inhibitors", Cosmetic & Toiletries, 100:69-72, 1985	☐
/ZF/	3	McCarthy, et al., "The Effect of Zinc Ions on the Antimicrobial Activity of Selected Preservatives", Journal of Pharmacy and Pharmacology, Vol. 41 (1989)	☐
/ZF/	4	PCT International Preliminary Report On Patentability for corresponding application PCT/US2007/079094 with mailing date December 11, 2008	☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	12441995
	Filing Date	2009-03-19
	First Named Inventor	Masood A. Chowhan
	Art Unit	
	Examiner Name	
	Attorney Docket Number	2667 US F

/ZF/	5	PCT International Search Report for corresponding application PCT/US2007/079094 with mailing date April 2, 2008	☐
/ZF/	6	PCT Written Opinion for corresponding application PCT/US2007/079094 with mailing date April 2, 2008	☐
/ZF/	7	Zeelie, et al., "Effects of Copper and Zinc Ions on the Germicidal Properties of Two Popular Pharmaceutical Antiseptic Agents, Cetylpyridinium Chloride and Povidone-iodine", Analyst, 123:503-507 (March 1998)	☐
/ZF/	8	Zeelie, et al., "The Effects of Selected Metal Salts on the Microbial Activities of Agents used in the Pharmaceutical and Related Industries", Metal Compounds in Environment and Life, 4:193-200 (1992)	☐

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature	/Zohreh Fay/ (06/21/2010)	Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Masood A. Chowhan et al.

U.S. Serial No.: 12/441,995

Confirmation No.: 7046

Filed: March 19, 2009

Examiner: Fay, Zohreh A.

Group Art Unit: 1627

CERTIFICATE OF FILING VIA EFS-WEB

I hereby certify that this correspondence is being submitted to the Mail Stop Amendment; Commissioner for Patents, P.O. Box 1450, Alexandria, VA. 22313-1450 via EFS-Web on this date:

December 17, 2010

By: /Barbara McKenzie/
Barbara McKenzie

For: SELF PRESERVED AQUEOUS PHARMACEUTICAL COMPOSITIONS

AMENDMENT AND RESPONSE

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir or Madam:

This paper is submitted in response to the Office Action dated June 24, 2010, for which the three-month date for response was September 24, 2010. Applicants submit herewith a request for a three-month extension of time to respond along with the required fee. This three-month extension will bring the due date to December 24, 2010. Should any request or fee be deficient or absent, consider this paragraph such a request and authorization to deduct said fees from Alcon Research, Ltd. Deposit Account No. 010682.

Reconsideration of the application is respectfully requested.

Amendments to the Claims are reflected in the listing of claims that begins on page 2 of this paper.

Remarks begin on page 6 of this paper.

REMARKS

The Office Action of June 24, 2010 rejected claims 1, 3-6 and 8-10. By this Amendment, Applicants have amended claims 3, 6 and 8 and added new claims 11-22. Applicants request reconsideration of the claims of the present application based on the discussion below.

I. Claim Rejections under 35 USC 102

The Office Action rejected claims 1, 3-6 and 8-10 under 35 USC 102 as being anticipated by U.S. Patent Application No. 2002/0123482 (Chowhan et al.). Applicants traverse these rejections and explain the patentability of these claims below. Applicants request reconsideration of the patentability of these claims based upon the discussion below.

Chowhan et al. discuss, in paragraph 13, employing zinc "at a concentration between about 0.005 and about 0.015 mmol/l". The lower limit of ZnCl in the claims of the present application is 0.0005 w/v %. This lower limit is equivalent to a concentration 0.0367 mmol/l of zinc in the composition. Thus, the lower limit in the claims of the present application provides zinc ions at a concentration that is at least double the upper limit cited in Chowhan et al. Chowhan et al. do not anticipate the claims of the present application.

Further, Chowhan et al. do not suggest the use of zinc ions for the enhancement of antimicrobial activity. Thus, the skilled artisan would not adjust the concentration of zinc ions based upon the teaching of Chowhan et al.

II. New Claims

In new claims 11-22, the preservative system is recited as consisting essentially of borate, polyol and zinc within particular concentrations in the composition. This preservative system is specifically stated as being sufficient to allow the composition to satisfy USP 26 preservative efficacy requirements. Chowhan et al. do not provide a composition that relies substantially entirely on borate, polyol and zinc for satisfying USP 26 preservative efficacy requirements. Further, Chowhan et al. do not suggest the possibility of such a system.

Claims 11-22 of the present application further recite a therapeutic agent that is selected from beta-blockers, carbonic anhydrase inhibitors, prostaglandin analogs, neuroprotectants, anti-angiogenesis agents, quinolones, anti-inflammatory agents, growth factors, immunosuppressant agents and anti-allergic agents. Chowhan et al. do not disclose the inclusion of any such therapeutic agent. Rather, Chowhan et al. disclose artificial tears.

CONCLUSION:

Applicants respectfully request reconsideration of the patentability of the claims of the present application. Should the Examiner have any questions regarding this Amendment, please feel free to contact the undersigned attorney at the phone number listed below.

Respectfully submitted,

ALCON RESEARCH, LTD.

December 17, 2010
Date

Scott A. Chapple, Agent
Reg. No. 46,287

Address for Correspondence:
Scott A. Chapple
Alcon Research, Ltd.
6201 S. Freeway, Mail Code TB4-8
Fort Worth, TX 76134-2099
Phone: 817-615-5288

Attorney Docket: 2667 US F

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Masood A. Chowhan et al.

U.S. Serial No.: 12/441,995

Confirmation No.: 7046

Filed: March 19, 2009

Examiner: Fay, Zohreh A.

Group Art Unit: 1627

CERTIFICATE OF FILING VIA EFS-WEB

I hereby certify that this correspondence is being submitted to the Mail Stop Amendment; Commissioner for Patents, P.O. Box 1450, Alexandria, VA. 22313-1450 via EFS-Web on this date:

December 17, 2010.

By: /Barbara McKenzie/
Barbara McKenzie

For: SELF PRESERVED AQUEOUS PHARMACEUTICAL COMPOSITIONS

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT PURSUANT TO 37 C.F.R. §1.97 (c) and FEE PURSUANT TO 37C.F.R. § 1.17 (p)

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Pursuant to the duty of disclosure under 37 C.F.R. § 1.97(c), Applicants submit the attached PTO Form 1449. Neither a final Office Action under §1.113 nor a notice of allowance under §1.311 have been issued in the above-referenced application.

Because the PTO has waived the requirement under 37 CFR 1.98(a)(2) to submit copies of each cited U.S. patent and patent application publication in all U.S. national patent applications filed after June 30, 2003, none are enclosed. Only copies of cited foreign patent documents and non-patent literature are enclosed.

Applicants request that the listed references be considered during prosecution of this application, and that the references appear among the "References Cited" on any patent issuing herefrom.

Applicants further draw the Examiner's attention to copending U.S. Patent Application Serial No. 11/858,781 and its ongoing prosecution.

The requisite fee under 37 C.F.R. §1.17(p) has been charged to Deposit Account No. 010682 via EFS Web.

Respectfully submitted,

December 17, 2010
Date

Scott A. Chapple
Registration No. 46,287

Address for Correspondence:
Alcon Research, Ltd.
Attn: Scott A. Chapple
6201 S. Freeway, TB4-8
Fort Worth, TX 76134-2099
Phone: 817-615-5288

Attorney Docket: 2667 US F

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	12441995
Filing Date	2009-03-19
First Named Inventor	Masood A. Chowhan
Art Unit	1627
Examiner Name	Fay, Zohreh A.
Attorney Docket Number	2667 US F

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	5130298		1992-07-14	Cini et al.	
	2	5820822		1998-10-13	Kross	
	3	7074827		2006-07-11	Ueno	
	4	7445771		2008-11-04	Dassanayake et al.	

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Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20060205725		2006-09-14	Ueno	
	2	20080075790		2008-03-27	Kabra et al.	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	12441995
Filing Date	2009-03-19
First Named Inventor	Masood A. Chowhan
Art Unit	1627
Examiner Name	Fay, Zohreh A.
Attorney Docket Number	2667 US F

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] ¡	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	98/10773	WO		1998-03-19	Richter Gedeon Vegyészeti		☐
	2	2007/106723	WO		2007-09-20	Bausch & Lomb Incorporated		☐
	3	2008/036847	WO		2008-03-27	Alcon Manufacturing, Ltd.		☐

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Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	Bruce Grahn et al., "Zinc and the Eye", JOURNAL OF THE AMERICAN COLLEGE OF NUTRITION, 106-118, 4-2001	☐

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[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	12441995
	Filing Date	2009-03-19
	First Named Inventor	Masood A. Chowhan
	Art Unit	1627
	Examiner Name	Fay, Zohreh A.
	Attorney Docket Number	2667 US F

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☒ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Scott A. Chapple, Reg. #46,287/	Date (YYYY-MM-DD)	2010-12-17
Name/Print	Scott A. Chapple	Registration Number	46,287

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

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3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Patent Application Fee Transmittal

Application Number:	12441995
Filing Date:	19-Mar-2009
Title of Invention:	SELF PRESERVED AQUEOUS PHARMACEUTICAL COMPOSITIONS
First Named Inventor/Applicant Name:	Masood A. Chowhan
Filer:	Scott Chapple/Barbara McKenzie
Attorney Docket Number:	2667 US F

Filed as Large Entity

U.S. National Stage under 35 USC 371 Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Independent claims in excess of 3	1614	1	220	220
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension - 3 months with $0 paid	1253	1	1110	1110
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
		Total in USD ($)		**1510**

Electronic Acknowledgement Receipt

EFS ID:	9060735
Application Number:	12441995
International Application Number:	
Confirmation Number:	7046
Title of Invention:	SELF PRESERVED AQUEOUS PHARMACEUTICAL COMPOSITIONS
First Named Inventor/Applicant Name:	Masood A. Chowhan
Customer Number:	26356
Filer:	Scott Chapple/Barbara McKenzie
Filer Authorized By:	Scott Chapple
Attorney Docket Number:	2667 US F
Receipt Date:	17-DEC-2010
Filing Date:	19-MAR-2009
Time Stamp:	12:37:51
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$1510
RAM confirmation Number	11799
Deposit Account	010682
Authorized User	

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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		2667_US_F_Resp-Amend_121710.pdf	308298 870774889cf31bda50387e819a751b42ebaa05c3	yes	8

Multipart Description/PDF files in .zip description

Document Description	Start	End
Amendment/Req. Reconsideration-After Non-Final Reject	1	1
Claims	2	5
Applicant Arguments/Remarks Made in an Amendment	6	8

Warnings:					
Information:					
2	Transmittal Letter	2667_US_F_IDS-S1_121710.pdf	75448 e4c83bf1ef57203640bb02474d297f9ebcdc5f04	no	2
Warnings:					
Information:					
3	Information Disclosure Statement (IDS) Filed (SB/08)	2667_US_F_IDS-S1_sb08_121710.pdf	612887 fd1d6e7b765ba6dfe56d96d0108e286fba961f40	no	4
Warnings:					
Information:					
4	Foreign Reference	WO_98_010773_A1.pdf	1094400 70ef6115f96fbb92512528529584633aa07adcb9	no	31
Warnings:					
Information:					
5	Foreign Reference	WO_07_106723_A2.pdf	2197756 e0118b98dd4e75ee4e52c42fdb4171cc8ae4b675	no	54
Warnings:					
Information:					
6	Foreign Reference	WO_08_036847_A2.pdf	1979616 49a025dda4e26b403fb1457c80745ccb493ea564	no	45
Warnings:					

Information:					
7	NPL Documents	Bruce_et_aL_2001_JACN_106-118.pdf	1046135 d88da65a732fa5caf3e1fea4d70c60a9cc0b3a34	no	13
Warnings:					
Information:					
8	Fee Worksheet (PTO-875)	fee-info.pdf	34116 de389587d84a163ab8c825de4f6b50cea4e99d9b	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	7348656	

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions and listings of claims in the application:

Claim 1 (previously presented): A multi-dose, self-preserved ophthalmic composition, said composition comprising an antimicrobial effective amount of a preservative system comprising 0.5 to 6.0 wt. % of a borate/polyol complex and zinc ions provided in the form of zinc chloride at a concentration of from 0.0005 to 0.005 w/v %.

Claim 2 (canceled)

Claim 3 (currently amended): A composition according to Claim 1, wherein the composition is an aqueous ophthalmic solution having sufficient antimicrobial activity to satisfy USP 26 preservative efficacy requirements.

Claim 4 (original): A composition according to Claim 1, wherein the composition does not contain a conventional antimicrobial preservative.

Claim 5 (original): A composition according to Claim 1, further comprising at least one therapeutically active agent.

Claim 6 (currently amended): A method of enhancing the antimicrobial activity of an aqueous ophthalmic pharmaceutical composition, which comprises including an antimicrobial effective amount of a preservative system in the composition, the preservative system comprising 0.5 to 6.0 wt.% of a borate/polyol complex and zinc ions provided in the form of zinc chloride at a concentration of from 0.0005 to 0.005 w/v % .

Claim 7 (canceled)

Claim 8 (currently amended): A method according to Claim 6, wherein the composition is a multidose, self preserved ophthalmic solution having sufficient antimicrobial activity to satisfy USP 26 preservative efficacy requirements.

Claim 9 (original): A method according to Claim 8, wherein the composition does not contain a conventional antimicrobial agent.

Claim 10 (original): A method according to Claim 6, wherein the composition contains a least one therapeutically active agent.

Claim 11. (new) A multi-dose, self-preserved ophthalmic composition, said composition comprising:

a therapeutically effective amount of an ophthalmic therapeutic agent selected from the group consisting of beta-blockers, carbonic anhydrase inhibitors, prostaglandin analogs, neuroprotectants, anti-angiogenesis agents, quinolones, anti-inflammatory agents, growth factors, immunosuppressant agents and anti-allergic agents; and

a preservative system consisting essentially of:

i. borate at a concentration in the composition of 0.3 to 1.5 w/v% wherein the borate comprises one or more borates;
ii. polyol at a concentration in the composition of 0.6 to 2.0 w/v% wherein the polyol comprises one or more polyols; and
iii. zinc ions, wherein the zinc ions are provided by zinc chloride at a concentration in the composition of 0.0005 to 0.005 w/v %;

wherein the borate and polyol form a borate/polyol complex for enhancing the antimicrobial activity of the composition and wherein the preservative system has sufficient antimicrobial activity to allow the composition to satisfy USP 26 preservative efficacy requirements.

Claim 12 (new): A composition as in claim 11 wherein the one or more polyols comprises sorbitol.

Claim 13 (new): A composition as in claim 11 wherein the one or more polyols comprises polyethylene glycol.

Claim 14 (new): A composition as in claim 11 wherein the therapeutic agent is a prostaglandin analog and the one or more polyols is selected from the group consisting of sorbitol, polyethylene glycol or a combination thereof.

Claim 15 (new): A composition as in claim 11 wherein the therapeutic agent is travoprost.

Claim 16 (new): A composition as in claim 15 wherein the one or more polyols comprises sorbitol and polyethylene glycol.

Claim 17 (new) A method of enhancing the antimicrobial activity of an aqueous ophthalmic pharmaceutical composition that, which comprises including a preservative system in the composition, the preservative system consisting essentially of:

i. borate at a concentration in the composition of 0.3 to 1.5 w/v% wherein the borate comprises one or more borates;
ii. polyol at a concentration in the composition of 0.6 to 2.0 w/v% wherein the polyol comprises one or more polyols; and
iii. zinc ions, wherein the zinc ions are provided by zinc chloride at a concentration in the composition of 0.0005 to 0.005 w/v %;

wherein:

i. the borate and polyol form a borate/polyol complex for enhancing the antimicrobial activity of the composition;
ii. the preservative system has sufficient antimicrobial activity to allow the composition to satisfy USP 26 preservative efficacy requirements; and
iii. the composition includes a therapeutically effective amount of an ophthalmic therapeutic agent selected from the group consisting of beta-blockers, carbonic anhydrase inhibitors, prostaglandin analogs, neuroprotectants, anti-angiogenesis agents, quinolones, anti-inflammatory agents, growth factors, immunosuppressant agents and anti-allergic agents.

Claim 18 (new): A method as in claim 17 wherein the one or more polyols comprises sorbitol.

Claim 19 (new): A method as in claim 17 wherein the one or more polyols comprises polyethylene glycol.

Claim 20 (new): A method as in claim 17 wherein the therapeutic agent is a prostaglandin analog and the one or more polyols is selected from the group consisting of sorbitol, polyethylene glycol or a combination thereof.

Claim 21 (new): A method as in claim 17 wherein the therapeutic agent is travoprost.

Claim 22 (new): A composition as in claim 21 wherein the one or more polyols comprises sorbitol and polyethylene glycol.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/441,995	03/19/2009	Masood A. Chowhan	2667 US F	7046

26356 7590 02/02/2011

ALCON
IP LEGAL, TB4-8
6201 SOUTH FREEWAY
FORT WORTH, TX 76134

EXAMINER	
FAY, ZOHREH A	

ART UNIT	PAPER NUMBER
1627	

MAIL DATE	DELIVERY MODE
02/02/2011	PAPER

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.

Interview Summary	Application No.	Applicant(s)	
	12/441,995	CHOWHAN ET AL.	
	Examiner	Art Unit	
	ZOHREH A. FAY	1627	

All participants (applicant, applicant's representative, PTO personnel):

(1) *ZOHREH A. FAY*. (3)_____.

(2) *Scott Chapple*. (4)_____.

Date of Interview: *27 January 2011*.

Type: a)☒ Telephonic b)☐ Video Conference
c)☐ Personal [copy given to: 1)☐ applicant 2)☐ applicant's representative]

Exhibit shown or demonstration conducted: d)☐ Yes e)☐ No.
If Yes, brief description: _____.

Claim(s) discussed: *All*.

Identification of prior art discussed: *All*.

Agreement with respect to the claims f)☐ was reached. g)☐ was not reached. h)☐ N/A.

Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: *The anticipation rejection was discussed. Applicant explained the differences between the Chowhan reference and the claimed invention*.

(A fuller description, if necessary, and a copy of the amendments which the examiner agreed would render the claims allowable, if available, must be attached. Also, where no copy of the amendments that would render the claims allowable is available, a summary thereof must be attached.)

THE FORMAL WRITTEN REPLY TO THE LAST OFFICE ACTION MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a reply to the last Office action has already been filed, APPLICANT IS GIVEN A NON-EXTENDABLE PERIOD OF THE LONGER OF ONE MONTH OR THIRTY DAYS FROM THIS INTERVIEW DATE, OR THE MAILING DATE OF THIS INTERVIEW SUMMARY FORM, WHICHEVER IS LATER, TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW. See Summary of Record of Interview requirements on reverse side or on attached sheet.

/Zohreh A Fay/ Primary Examiner, Art Unit 1627	

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews
Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:

1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/441,995	03/19/2009	Masood A. Chowhan	2667 US F	7046

26356 7590 03/14/2011

ALCON
IP LEGAL, TB4-8
6201 SOUTH FREEWAY
FORT WORTH, TX 76134

EXAMINER	
FAY, ZOHREH A	

ART UNIT	PAPER NUMBER
1627	

MAIL DATE	DELIVERY MODE
03/14/2011	PAPER

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.

Office Action Summary	Application No.	Applicant(s)	
	12/441,995	CHOWHAN ET AL.	
	Examiner	Art Unit	
	ZOHREH FAY	1627	

-- 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 *17 December 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ 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

4)☒ Claim(s) *1,3-6 and 8-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-6 and 8-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ 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).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

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).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ 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) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/17/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Claims 1, 3-6 and 8-22 are pending in the instant application.

The amendments and remarks filed on December 17, 2010 have been received and entered.

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 negatived 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 1, 3-6 and 8-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chowhan et al. (2002/0123482) in view of WO Patent 2007/1063634.

Chowhan et al. teach a multidose self preserved ophthalmic composition comprising 0.5 to 6% borax/polyol complex and zinc ion in the form of Zinc chloride in combination with an active ingredient, such as amino acids. See Para [0013], Para [0020], Para [0021] and claims 15-16. Chowhan differs from the claimed invention in the concentrations of zinc chloride and specific active ingredients. The WO patent teaches the use of a Zinc-based preservative in an ophthalmic formulation with the improved safety and comfort. See page 1, lines 1-7. the concentrations encompassing the claimed concentrations are taught on page 7, lines 9-11. The use of therapeutic agents, such as anti-inflammatory agents and immunosuppressive agents are taught in page 9, lines 1-6. It would have been obvious to a person skilled in the art to use the claimed range concentrations for Zinc motivated by the teachings of WO Patent which teaches the use of such concentrations in ophthalmic formulations as old and well known. The motivation for adding the secondary components is also provided by WO Patent, which teaches the addition of the claimed active ingredients to a preserved zinc-based ophthalmic formulation as old and well known.

Applicant's submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on December 17, 2010 prompted the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 609.04(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ZOHREH FAY whose telephone number is (571)272-0573. The examiner can normally be reached on Monday to Friday 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni 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). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

ZF
/Zohreh A Fay/
Primary Examiner, Art Unit 1627

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12441995	CHOWHAN ET AL.
	Examiner	Art Unit
	ZOHREH A FAY	1612

SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
West	6/19/2010	ZF
Inventor search	6/19/2010	ZF
updated	3/9/2011	ZF

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12441995	CHOWHAN ET AL.
	Examiner	**Art Unit**
	ZOHREH A FAY	1612

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	06/21/2010	03/09/2011							
	1	✓	✓							
	2	✓	-							
	3	✓	✓							
	4	✓	✓							
	5	✓	✓							
	6	✓	✓							
	7	-	-							
	8	✓	✓							
	9	✓	✓							
	10	✓	✓							
	11		✓							
	12		✓							
	13		✓							
	14		✓							
	15		✓							
	16		✓							
	17		✓							
	18		✓							
	19		✓							
	20		✓							
	21		✓							
	22		✓							

Doc code: RCEX
Doc description: Request for Continued Examination (RCE)

PTO/SB/30EFS (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL
(Submitted Only via EFS-Web)

Application Number	12441995	Filing Date	2009-03-19	Docket Number (if applicable)	2667 US F	Art Unit	1627
First Named Inventor	Masood A. Chowhan			Examiner Name	Fay, Zohreh A.		

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. The Instruction Sheet for this form is located at WWW.USPTO.GOV

SUBMISSION REQUIRED UNDER 37 CFR 1.114

Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

- ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
- ☐ Other _____

☒ Enclosed

- ☒ Amendment/Reply
- ☒ Information Disclosure Statement (IDS)
- ☐ Affidavit(s)/ Declaration(s)
- ☐ Other _____

MISCELLANEOUS

☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of months _____ (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

☐ Other _____

FEES

☐ **The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.**
The Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to Deposit Account No _____

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

☒ Patent Practitioner Signature

☐ Applicant Signature

PTO/SB/30EFS (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Signature of Registered U.S. Patent Practitioner			
Signature	/Scott A. Chapple, Reg. #46,287/	Date (YYYY-MM-DD)	2011-07-12
Name	Scott A. Chapple	Registration Number	46287

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Masood A. Chowhan et al.	)	Examiner: Fay, Zohreh A.
	)	
Serial No: 12/441,995 (Conf. #7046)	)	Group Art Unit: 1627
	)	
Filed: March 19, 2009	)	Docket No.: 2667 US F

FOR: Self Preserved Aqueous Pharmaceutical Compositions

SECOND SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT PURSUANT TO 37 C.F.R. §§ 1.56, 1.97, 1.98 and FEE PURSUANT TO 37C.F.R. § 1.17 (p)

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Pursuant to the duty of disclosure under 37 C.F.R. §1.56, Applicant directs the attention of the Examiner to the seven (7) references listed on the attached Form PTO/SB08a.

This Information Disclosure Statement includes an article and an illustration of packaging for a product named Systane Free Lubricant Eye Drops Liquid Gel, which was previously marketed in the United States for a limited time by Alcon Laboratories, Inc. ("Alcon"). It is believed that Alcon's first commercial sale of this product occurred on or about December 14, 2005. The product is not currently sold; it was withdrawn from the market in or around December 2006. The formulation of the product was as follows:

Component	Concentration	Units
Hydroxypropyl Guar 8a	0.16% to 0.19%	W/V %
Boric Acid	0.7%	W/V %
Sorbitol	1.4%	W/V %
Polyethylene Glycol (400)	0.4%	W/V %
Propylene Glycol	0.3%	W/V %
Potassium Chloride	0.12%	W/V %
Sodium Chloride	0.1%	W/V %
Calcium Chloride (Dihydrate)	0.0053%	W/V %
Magnesium Chloride (Hexahydrate)	0.0064%	W/V %
Zinc Chloride	0.0015%	W/V %
2-Amino-2-Methyl-Propanol (Amp)	0.57%	W/V %

Hydrochloric Acid (1n)	0.15%	W/V %
Sodium Hydroxide	adjust pH to 7.9	W/V %
Purified Water	qs to 100%	W/V %

Formulation Comments:

$ZnCl_2$ may be added in up to 5% xs to compensate for manufacturing losses.

It is believed that no fee is required to make this a complete and timely filing. However, if it is determined that a petition or fee is required, the Commissioner is hereby authorized to charge any fee associated with this statement to our Deposit Account No. 010682.

Applicants respectfully request that the listed references be considered during prosecution of this application, and that the references appear among the References Cited on any patent issuing herefrom.

Respectfully submitted,

July 12, 2011
Date

Scott A. Chapple
Registration No. 46,287

Address for Correspondence:
Alcon Research, Ltd.
Attn: Scott A. Chapple
6201 S. Freeway, TB4-8
Fort Worth, TX 76134-2099
Phone: 817-615-3288

Attorney Docket: 2667 US P

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	12441995
Filing Date	2009-03-19
First Named Inventor	Masood A. Chowhan
Art Unit	1627
Examiner Name	Fay, Zohreh A.
Attorney Docket Number	2667 US F

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	5460834		1995-10-24	Bhagat	

If you wish to add additional U.S. Patent citation information please click the Add button. Add

U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20050214382		2005-09-29	Xia et al.	
	2	20070212420		2007-09-13	Xia et al.	
	3	20070297990		2007-12-27	Shah et al.	
	4	20100227003		2010-09-09	Shah et al.	

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FOREIGN PATENT DOCUMENTS Remove

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] ¡	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	12441995
	Filing Date	2009-03-19
	First Named Inventor	Masood A. Chowhan
	Art Unit	1627
	Examiner Name	Fay, Zohreh A.
	Attorney Docket Number	2667 US F

	1							☐

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NON-PATENT LITERATURE DOCUMENTS Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	GUTTMAN, "Liquid gel therapy broadens role of dry eye product line", Ophthalmologytimes.com, 2006, pgs 33-34 and copyright notice	☐
	2	Illustration of packaging for Systane® free	☐

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	12441995
	Filing Date	2009-03-19
	First Named Inventor	Masood A. Chowhan
	Art Unit	1627
	Examiner Name	Fay, Zohreh A.
	Attorney Docket Number	2667 US F

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☒ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Scott A. Chapple, Reg. #46,287/	Date (YYYY-MM-DD)	2011-07-12
Name/Print	Scott A. Chapple	Registration Number	46,287

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Patent Application Fee Transmittal

Application Number:	12441995
Filing Date:	19-Mar-2009
Title of Invention:	SELF PRESERVED AQUEOUS PHARMACEUTICAL COMPOSITIONS
First Named Inventor/Applicant Name:	Masood A. Chowhan
Filer:	Scott Chapple/Barbara McKenzie
Attorney Docket Number:	2667 US F

Filed as Large Entity

U.S. National Stage under 35 USC 371 Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 1 month with $0 paid	1251	1	130	130

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Request for continued examination	1801	1	810	810
		Total in USD ($)		**940**

Electronic Acknowledgement Receipt

EFS ID:	10497853
Application Number:	12441995
International Application Number:	
Confirmation Number:	7046
Title of Invention:	SELF PRESERVED AQUEOUS PHARMACEUTICAL COMPOSITIONS
First Named Inventor/Applicant Name:	Masood A. Chowhan
Customer Number:	26356
Filer:	Scott Chapple/Barbara McKenzie
Filer Authorized By:	Scott Chapple
Attorney Docket Number:	2667 US F
Receipt Date:	12-JUL-2011
Filing Date:	19-MAR-2009
Time Stamp:	12:22:25
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$940
RAM confirmation Number	9720
Deposit Account	010682
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. 1.492 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		2667_US_F_Amend-w-RCE_071211.pdf	390454 b23c1d5ceaae5e7fbe808f9bb7eb1556f19d0c6f	yes	9

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment Submitted/Entered with Filing of CPA/RCE	1	1
	Claims	2	4
	Applicant Arguments/Remarks Made in an Amendment	5	9

Warnings:					
Information:					
2	Request for Continued Examination (RCE)	2667_US_F_RCE_071211.pdf	697973 11a49f05d9d40060ea49f83bf2cfa811a8c0f820	no	3
Warnings:					
Information:					
3	Transmittal Letter	2667_US_F_IDS-S2_071211.pdf	85620 53b2a7b524118abb47c9fdaa87a76b258ebbeb96	no	2
Warnings:					
Information:					
4	Information Disclosure Statement (IDS) Form (SB08)	2667_US_F_IDS-S2_08a_071211.pdf	612674 d011418651427 9f9b4072c73e610ac23d803fdaf	no	4
Warnings:					
Information:					
5	Non Patent Literature	GUTTMAN_2006_OphthalmologyTimes.pdf	317495 fbd8f87e6f130a7d13891e754fe1214a2957fc62	no	3
Warnings:					
Information:					
6	Non Patent Literature	Systane_Free_Packaging.pdf	117195 904505e9423f466bbc071a7252b4a37b737d34f5	no	1
Warnings:					

Information:					
7	Fee Worksheet (SB06)	fee-info.pdf	32792 be81463112b0897d9b3a082106a81312cbc05841	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	2254203	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Masood A. Chowhan et al.

U.S. Serial No.: 12/441,995

Confirmation No.: 7046

Filed: March 19, 2009

Examiner: Fay, Zohreh A.

Group Art Unit: 1627

CERTIFICATE OF FILING VIA EFS-WEB

I hereby certify that this correspondence is being submitted to the Mail Stop RCE; Commissioner for Patents, P.O. Box 1450, Alexandria, VA. 22313-1450 via EFS-Web on this date: July 12, 2011.

By: /Barbara McKenzie/
Barbara McKenzie

For: SELF PRESERVED AQUEOUS PHARMACEUTICAL COMPOSITIONS

AMENDMENT AND RESPONSE BEING FILED WITH A REQUEST FOR CONTINUED EXAMINATION

Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir or Madam:

This paper is submitted in response to the Office Action dated March 14, 2011, for which the Examiner has set a three-month period for response. A petition for a one month extension of time and the requisite fee are submitted herewith, thus making the response due on or before July 14, 2011. A Request for Continued Examination is being filed concurrently herewith to deduct said fees from Alcon Research, Ltd. Deposit Account No. 010682.

Reconsideration of the application is respectfully requested.

Amendments to the Claims are reflected in the listing of claims that begins on page 2 of this paper.

Remarks begin on page 6 of this paper.

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions and listings of claims in the application:

Claims 1-10 (canceled)

Claim 11 (currently amended): A multi-dose, self-preserved ophthalmic composition, said composition comprising:

a therapeutically effective amount of an ophthalmic therapeutic agent selected from the group consisting of beta-blockers, carbonic anhydrase inhibitors, prostaglandin analogs, neuroprotectants, anti-angiogenesis agents, quinolones, anti-inflammatory agents, growth factors, immunosuppressant agents and anti-allergic agents; and

a preservative system consisting essentially of:

i. borate at a concentration in the composition of 0.3 to 1.5 w/v% wherein the borate comprises one or more borates;

ii. polyol at a concentration in the composition of 0.6 to 2.0 w/v% wherein the polyol comprises sorbitol and propylene glycol ~~one or more polyols~~; and

iii. zinc ions, wherein the zinc ions are provided by zinc chloride at a concentration in the composition of 0.0005 to 0.005 w/v %;

wherein the borate and polyol form a borate/polyol complex for enhancing the antimicrobial activity of the composition and wherein the preservative system has sufficient antimicrobial activity to allow the composition to satisfy USP 26 preservative efficacy requirements.

Claim 12 (canceled)

Claim 13 (canceled)

Claim 14 (currently amended): A composition as in claim 11 wherein the therapeutic agent is a prostaglandin analog ~~and the one or more polyols is selected from the group consisting of sorbitol, polyethylene glycol or a combination thereof~~.

Claim 15 (previously presented): A composition as in claim 11 wherein the therapeutic agent is travoprost.

Claim 16 (canceled)

Claim 17 (currently amended) A method of enhancing the antimicrobial activity of an aqueous ophthalmic pharmaceutical composition that, which comprises including a preservative system in the composition, the preservative system consisting essentially of:

i. borate at a concentration in the composition of 0.3 to 1.5 w/v% wherein the borate comprises one or more borates;
ii. polyol at a concentration in the composition of 0.6 to 2.0 w/v% wherein the polyol comprises sorbitol and propylene glycol ~~one or more polyols~~; and
iii. zinc ions, wherein the zinc ions are provided by zinc chloride at a concentration in the composition of 0.0005 to 0.005 w/v %;

wherein:

i. the borate and polyol form a borate/polyol complex for enhancing the antimicrobial activity of the composition;
ii. the preservative system has sufficient antimicrobial activity to allow the composition to satisfy USP 26 preservative efficacy requirements; and
iii. the composition includes a therapeutically effective amount of an ophthalmic therapeutic agent selected from the group consisting of beta-blockers, carbonic anhydrase inhibitors, prostaglandin analogs, neuroprotectants, anti-angiogenesis agents, quinolones, anti-inflammatory agents, growth factors, immunosuppressant agents and anti-allergic agents.

Claim 18 (canceled)

Claim 19 (canceled)

Claim 20 (currently amended): A method as in claim 17 wherein the therapeutic agent is a prostaglandin analog ~~and the one or more polyols is selected from the group consisting of sorbitol, polyethylene glycol or a combination thereof~~.

Claim 21 (previously presented): A method as in claim 17 wherein the therapeutic agent is travoprost.

Claim 22 (canceled)

REMARKS

Applicants thank Examiner Faye for the courtesies extended to the undersigned during a personal interview conducted on May 10, 2011. The Office Action of March 14, 2011 rejected claims 1, 3-6 and 8-22. By this Amendment, Applicants have canceled claims 1, 3-6, 8-10, 12-13, 16, 18-19 and 22 and amended claims 11, 14, 17 and 20.

I. Claim Rejections under 35 USC 103

The Office Action did not specifically articulate rejections for any of previously pending claims 11-14 and 17-22. However, claim rejections that were made by the Office Action were based upon U.S. Patent Application No. 2002/0123482 (Chowhan et al.) in view of WO Patent 2007/1063634, which applicants believe to be WO 2007/106723 (Dobie et al).

In response to this rejection, Applicants recap the subject matter of the presentation given to Examiner Faye by the undersigned during the Interview. In particular, Applicants recap the many failures of the prior art to utilize low concentrations of zinc to preserve ophthalmic compositions. Applicants then provide reasoning why the currently pending claims are patentable over Chowhan et al. and Dobie et al. Applicants also remind Examiner Faye that it was agreed that she would phone the undersigned if she felt the claims still needed to be rejected so that such rejection could be discussed prior to issuance of another Office Action.

Prior Art Efforts

The present claims recite a preservation system consisting essentially of borate, particular polyols (sorbitol and propylene glycol) and zinc chloride. Thus, the composition and method of the claims of the present application rely exclusively or nearly exclusively upon only those ingredients to achieve preservation that passes USP standards Moreover, that combination of ingredients allows preservation according to USP standards with the low concentrations of zinc chloride recited in the claims. Such a preservation system is particularly desirable because it substantially reduces astringent effects caused by higher

concentrations of zinc. Further, there have been many prior art attempts to achieve preservation with low concentrations of zinc. However, each of these efforts has failed to achieve such preservation while using the preservation system of the claims of the present application which relies entirely or substantially entirely on a very low concentration of zinc and a particular combination of polyols to pass USP preservation. Applicants review those failures below as discussed during the Interview.

US Patent 5,597,559 to Olejnik et al. (hereinafter Olejnik et al.) uses zinc to create a preservative free ophthalmic composition. However, Olejnik et al. only achieve preservation for short periods of time (e.g., up to about 72 hours)(see col. 5, lines 1-15 of Olejnick et al.). Of course, USP preservation standards require that an ophthalmic composition show preservation efficacy for at 28 days past inoculation. As such, Olejnik et al. are far from the capability to pass USP with their ophthalmic compositions.

WO 2005/097067 to Xia et al. (hereinafter Xia et al.) attempts to use relatively low concentrations of Zinc to preserve ophthalmic compositions. However, the examples of Xia et al. suggest that they were only able to achieve preservation efficacy with zinc chloride at a concentration that is approximately 10 fold the concentration which is recited in the claims of the present application. In particular, example 20 of Xia et al. employs zinc chloride at a concentration of 0.05 wt%, which is approximately 10 fold the upper limit of the claims of the present application. Xia et al. provide no teaching of how to achieve preservation efficacy satisfying USP guidelines at the zinc chloride concentrations recited in the claims of the present application.

WO 2007/106723 to Dobie et al. (hereinafter Dobie et al.) also attempts to use relatively low concentrations of Zinc to preserve ophthalmic compositions. However, the examples of Dobie et al. suggest that they were only able to achieve preservation efficacy with zinc chloride at a concentration that is approximately 2 fold the concentration which is recited in the claims of the present application. In particular, example 7 of Dobie et al. employs zinc chloride at a concentration of 0.01 wt%, which is approximately 2 fold the upper limit of the claims of the present application. Dobie et al. provide no teaching of how to achieve preservation efficacy satisfying USP guidelines at the zinc chloride concentrations recited in the claims of the present application.

Lastly, there is submitted herewith in an information disclosure statement, documentation of a product referred to as Systane-Free (the "S-F documentation"). The S-F documentation discloses a product that employed a concentration of zinc chloride that is within the range recited in the claims of the present application and was able to pass USP preservation. However, Systane-Free employed a substantial amount of aminomethyl propanol (AMP) to achieve USP preservation. An article titled "Liquid Gel Therapy Broadens Role of Dry Eye Product Line" is cited in the information disclosure statement submitted herewith. Of Systane-Free, the article states, "it is formulated at a higher pH, dispenses as a thicker product, and uses a novel preservation system consisting of borate, sorbitol, aminomethyl propanol, and zinc ... Those four components create a hostile antimicrobial environment..." (see para. 2 of the article). Systane-free relied to a substantial extent upon the aminomethyl propanol for preservation efficacy. As such, Systane-Free does not contemplate or suggest a product that achieves USP preservation without AMP or without relying on something more than borate, polyols and zinc.

The Office Action rejection based upon Chowhan et al. in view of Dobie et al.

As suggested by the Office Action, Chowhan et al. do not teach the use of zinc chloride in the range recited by the claims of the present application. Rather, as discussed during the Interview, Chowhan et al. utilize zinc chloride in very small concentrations in order to make artificial tears that have a composition similar to that of natural human tears. Chowhan et al. substantially rely upon a preservative, as can be seen in the examples thereof, to preserve their composition.

Dobie et al. teach the utilization of zinc for its antimicrobial properties. However, as discussed with Examiner Faye during the Interview and as discussed above, Dobie et al. do not teach a composition that includes zinc chloride at the low concentrations recited in the claims of the present application and can pass USP preservation efficacy standards. Applicants find that the example on page 28 shows 0.01 w/v% as the lowest concentration of zinc chloride in Dobie et al. that passes preservation efficacy standards. As discussed during the Interview, Dobie et al. provide one of many examples of failures of the prior art to pass preservation efficacy standards with the low concentrations of zinc provided by the present application.

Further, the skilled artisan could not combine these references to arrive at the subject matter of the claims of the present application. In particular, substituting the preservation system of Chowhan et al. into Dobie et al. would result in a composition that would rely substantially upon a preservative for preservation efficacy and would thus be outside of the claims of the present application. Alternatively, substituting the preservation system of Dobie et al. into Chowhan et al. would result in a composition that includes amounts of zinc chloride that are substantially higher than those recited in the claims of the present application, relies upon additional ingredients other that borate, polyol and zinc for preservation and/or likely fails USP preservation efficacy standards.

In addition to the above, neither of the cited references instruct toward the specific combination of polyols (i.e., the combination of sorbitol and propylene glycol) that are now specifically recited in the claims. As suggested in the last line of page 7 and as shown in the examples of the present application, this combination of polyols aids in producing particularly desirable preservation efficacy when used in combination with with zinc and borate.

CONCLUSION:

Applicants respectfully request reconsideration of the patentability of the claims of the present application. Should the Examiner have any questions regarding this Amendment, please feel free to contact the undersigned attorney at the phone number listed below.

Respectfully submitted,

ALCON RESEARCH, LTD.

July 12, 2011
Date

Scott A. Chapple, Agent
Reg. No. 46,287

Address for Correspondence:
Scott A. Chapple
Alcon Research, Ltd.
6201 S. Freeway, Mail Code TB4-8
Fort Worth, TX 76134-2099
Phone: 817-615-5288

Attorney Docket: 2667.US.P

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 12/441,995	Filing Date 03/19/2009	☐ To be Mailed

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY ☐		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	07/12/2011	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 6	Minus	** 20	= 0	X $ =		OR	X $52=	0
	Independent (37 CFR 1.16(h))	* 2	Minus	***3	= 0	X $ =		OR	X $220=	0
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	0

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/DORIS BURNS/

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

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UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/441,995	03/19/2009	Masood A. Chowhan	2667 US F	7046

26356 7590 09/16/2011

ALCON
IP LEGAL, TB4-8
6201 SOUTH FREEWAY
FORT WORTH, TX 76134

EXAMINER	
FAY, ZOHREH A	

ART UNIT	PAPER NUMBER
1627	

MAIL DATE	DELIVERY MODE
09/16/2011	PAPER

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.

Office Action Summary	Application No.	Applicant(s)
	12/441,995	CHOWHAN ET AL.
	Examiner	Art Unit
	ZOHREH FAY	1627

-- 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 *12 July 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ 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

4)☒ Claim(s) *11,14,15,17,20 and 21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11,14,15,17,20 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ 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).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

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).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ 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)	4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) ☐ Notice of Informal Patent Application
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/17/2010, 7/12/2011*.	6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 12, 2011 has been entered.

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 negatived 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 1, 3-6 and 8-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chowhan et al. (2002/0123482) in view of WO Patent 2007/106723.

Chowhan et al. teach a multidose self preserved ophthalmic composition comprising 0.5 to 6% borax/polyol complex and zinc ion in the form of Zinc chloride in combination with an active ingredient, such as amino acids. See Para [0013], Para [0020], Para [0021] and claims 15-16. The use of sorbitol and propylene glycol is taught in Para [0023]. Chowhan differs from the claimed invention in the concentrations of zinc chloride and specific active ingredients. The WO patent teaches the use of a Zinc-based preservative in an ophthalmic formulation with the improved safety and comfort. See page 1, lines 1-7. The concentrations encompassing the claimed concentrations are taught on page 7, lines 9-11. The use of therapeutic agents, such as anti-inflammatory agents and immunosuppressive agents are taught in page 9, lines 1-6. It would have been obvious to a person skilled in the art to use the claimed range concentrations for Zinc motivated by the teachings of WO Patent which teaches the use of such concentrations in ophthalmic formulations as old and well known. The motivation for adding the secondary components is also provided by WO Patent, which

teaches the addition of the claimed active ingredients to a preserved zinc-based ophthalmic formulation as old and well known.

Applicant's arguments and remarks have been carefully considered, but are not deemed to be persuasive. Applicant in his remarks argues the higher concentrations of zinc chloride, at least 2 fold higher of the WO patent in comparison with the lowe concentrations of zinc claimed by the instant application. The arguments have been noted. It is the examiner's position that the WO patent on page 7 teaches a zinc compound at the claimed range concentrations. Applicant particularly refers to example 7 of the WO patent to show the higher concentration of zinc compound. It is the examiner's position that the concentrations in example 7 are cited as w/w, however, the concentrations of zinc in the instant claims are w/v.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ZOHREH FAY whose telephone number is (571)272-0573. The examiner can normally be reached on Monday to Friday 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni 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). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

ZF
/Zohreh A Fay/
Primary Examiner, Art Unit 1627

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	12441995
Filing Date	2009-03-19
First Named Inventor	Masood A. Chowhan
Art Unit	1627
Examiner Name	Fay, Zohreh A.
Attorney Docket Number	2667 US F

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	5130298		1992-07-14	Cini et al.	
	2	5820822		1998-10-13	Kross	
	3	7074827		2006-07-11	Ueno	
	4	7445771		2008-11-04	Dassanayake et al.	

If you wish to add additional U.S. Patent citation information please click the Add button. Add

U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20060205725		2006-09-14	Ueno	
	2	20080075790		2008-03-27	Kabra et al.	

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FOREIGN PATENT DOCUMENTS Remove

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /ZF/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	12441995
Filing Date	2009-03-19
First Named Inventor	Masood A. Chowhan
Art Unit	1627
Examiner Name	Fay, Zohreh A.
Attorney Docket Number	2667 US F

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] ¡	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	98/10773	WO		1998-03-19	Richter Gedeon Vegyészeti		☐
	2	2007/106723	WO		2007-09-20	Bausch & Lomb Incorporated		☐
	3	2008/036847	WO		2008-03-27	Alcon Manufacturing, Ltd.		☐

If you wish to add additional Foreign Patent Document citation information please click the Add button [Add]

NON-PATENT LITERATURE DOCUMENTS [Remove]

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	Bruce Grahn et al., "Zinc and the Eye", JOURNAL OF THE AMERICAN COLLEGE OF NUTRITION, 106-118, 4-2001	☐

If you wish to add additional non-patent literature document citation information please click the Add button [Add]

EXAMINER SIGNATURE

Examiner Signature	/Zohreh Fay/ (03/09/2011)	Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /ZF/

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	12441995
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First Named Inventor	Masood A. Chowhan
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Examiner Name	Fay, Zohreh A.
Attorney Docket Number	2667 US F

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	5460834		1995-10-24	Bhagat	

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Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20050214382		2005-09-29	Xia et al.	
	2	20070212420		2007-09-13	Xia et al.	
	3	20070297990		2007-12-27	Shah et al.	
	4	20100227003		2010-09-09	Shah et al.	

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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /ZF/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	12441995
	Filing Date	2009-03-19
	First Named Inventor	Masood A. Chowhan
	Art Unit	1627
	Examiner Name	Fay, Zohreh A.
	Attorney Docket Number	2667 US F

	1							☐

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NON-PATENT LITERATURE DOCUMENTS Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	GUTTMAN, "Liquid gel therapy broadens role of dry eye product line", Ophthalmologytimes.com, 2006, pgs 33-34 and copyright notice	☐
	2	Illustration of packaging for Systane® free	☐

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature	/Zohreh Fay/ (07/28/2011)	Date Considered	

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[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /ZF/

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12441995	CHOWHAN ET AL.
	Examiner	Art Unit
	ZOHREH A FAY	1612

SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
West	6/19/2010	ZF
Inventor search	6/19/2010	ZF
updated	3/9/2011	ZF
updated	7/28/2011	ZF

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Masood A. Chowhan et al.

U.S. Serial No.: 12/441,995

Confirmation No.: 7046

Filed: March 19, 2009

Examiner: Fay, Zohreh A.

Group Art Unit: 1627

For: SELF PRESERVED AQUEOUS PHARMACEUTICAL COMPOSITIONS

CERTIFICATE OF FILING VIA EFS-WEB

I hereby certify that this correspondence is being submitted to the Mail Stop Amendment; Commissioner for Patents, P.O. Box 1450, Alexandria, VA. 22313-1450 via EFS-Web on this date:

December 13, 2011.

By: /Barbara McKenzie/
Barbara McKenzie

AMENDMENT AND RESPONSE

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir or Madam:

This paper is submitted in response to the Office Action dated September 16, 2011, for which the Examiner has set a three-month period for response.

Applicants believe that no extension of time is required. However, if the U.S. Patent Office deems any fees to be deficient or absent, consider this paragraph such a request and authorization to deduct said fees from Alcon Research, Ltd. Deposit Account No. **010682.**

Reconsideration of the application is respectfully requested.

A listing of claims begins on page 2 of this paper.

Remarks begin on page 5 of this paper.

REMARKS

The Office Action of September 16, 2011 rejected claims 11, 14, 15, 17, 20 and 21. By this Amendment, Applicants have added new claims 23-26.

I. Claim Rejections under 35 USC 103

The Office Action rejected claims 11, 14, 15, 17, 20 and 21 as being obvious and unpatentable over U.S. Patent Application No. 2002/0123482 (Chowhan et al.) in view of International Patent Application No. WO 2007/106723 (Dobie et al). Applicants respectfully traverse these rejections. Applicants respectfully request reconsideration of the patentability of the claims of the present application based upon the following discussion.

The previous Office Action issued for the present application rejected the previously pending claims as being obvious in view of the same references cited in the present Office Action, Chowhan et al. and Dobie et al. In response to the previous Office Action, Applicants amended the previously claims into their current form and provided an extensive discussion of why the presently pending claims are patentable over Chowhan et al. and Dobie et al. Applicants showed why Chowhan et al and Dobie et al. are not properly combinable as prior art. More importantly, however, Applicants showed that Chowhan et al. and Dobie et al. did not teach or suggest, even when combined with reasoning and common sense, the subject matter of the present claims to the skilled artisan. The present Office Action does not refute these showings, rather it seems to suggest that Applicants showing is not persuasive because of insufficient proof as discussed fully below.

In their previous response, Applicants showed that the combination of Chowhan et al. in view of Dobie et al. did not teach or suggest or provide any reasonable pathway for the skilled artisan to develop a composition caplable of passing the preservative efficacy requirements using a preservative system that consisted essentially of borate, polyol (particularly sorbitol and propylene glycol) and zinc chloride at the concentrations recited in the presently pending claims of the present application. More specifically, Applicants showed

that the cited prior art did not teach or suggest or provide any reasonable pathway as to how to pass preservative efficacy requirements using the aforementioned preservative system while maintaining the low concentrations of zinc chloride recited in the claims of the present application. Applicants specifically showed that Chowhan et al. did not rely on a system consisting essentially of zinc, borate and polyol, but rather relied upon additional antimicrobial aids. Applicants further showed that the lowest concentration of zinc that was able to pass preservative efficacy requirements in Dobie et al. was shown in example 7 thereof and that such concentration of zinc chloride in that example is approximately double that of the upper concentration of zinc chloride in the composition of the claims of the present application.

The present Office Action does not refute these showings from the Applicants. Rather it merely suggests that Applicants showing is not persuasive because the concentration of zinc chloride in example 7 of Dobie et al. is in w/w% or weight/weight percent while the concentration in Applicants claim is in w/v% or weight volume percent. The present Office Action puts forward no suggestion that Chowhan et al. and/or Dobie et al., singly or in combination, would suggest or provide a reasonable pathway to the skilled artisan as to how to achieve passing preservation efficacy with the system of the claims of the present application, which uses a very low concentration of zinc chloride.

As such, Applicants believe that the previously presented argument would be considered valid if Applicants can show that w/w% and w/v% for the Examples of Dobie et al. are substantially equivalent and that their original unrefuted argument is valid. Calculation of w/w% and w/v% for aqueous solutions is as follows:

w/w% of aqueous solution = (mass of solute in grams)/(mass of solution in grams) * 100

w/v% of aqueous solution = (mass of solute in grams)/(volume of solution in milliliters) * 100

Since the w/w% of a solution is going to be the same for any total weight of homogeneous solution, we can assume, for ease of calculation, 1 gram of solution of the formulation of example 7.

Example 7 therefore, in one gram of solution, includes:

.00115 grams of sodium borate
.005 grams of boric acid
0.01 grams of glycerin
0.0025 grams of sodium alginate
0.0001 grams of zinc chloride; and
0.0001 grams of magnesium chloride; and
.98115 grams of water since the remaining grams of the solution are water.

As can be seen from the breakdown above, the composition of example 7 is 98.115 % by weight water. As such, the density of the composition of example 7 will be extremely close to the density of water and the density of water is 1.0 gram per milliliter (ml).

Thus, 1.0 gram of the composition of example 7 is extremely close to 1.0 ml of the composition. In turn, this means that there is very near to 0.0001 grams of zinc chloride for every 1.0 ml of the composition of example 7. Then plugging this into the equation for w/v% yields the following:

w/v% = (mass of solute in grams)/(volume of solution in milliliters) * 100
w/v% = (0.0001 grams $ZnCl_2$)/(1 milliliters of solution) * 100 = 0.01 w/v%

Applicants understand that the w/v% of a solution is not exactly equal to the w/w% of a solution. However, Applicants and the skilled artisan also understand that, for the composition of example 7 of Dobie et al. and for all of the other exemplary compositions of Dobie et al., the w/w% of the solute in those compositions will be within less than 5% of the w/v% of that solute in those compositions. In other words, for a concentration of 0.01 w/w%, the w/v% will be no greater than 0.0105 and no less than 0.0095. As suggested above, this is

because each of the compositions of Dobie et al. is nearly entirely water and will have a density very close to 1.0 gram per milliliter.

Thus, as stated in applicants' previous response, the amount of $ZnCl_2$ in example 7 is approximately double the upper limit of concentration of $ZnCl_2$ recited in the claims of the present application.

Applicants have gone through the above calculation to illustrate that, for highly aqueous solutions such as those in Dobie et al., the w/v% of solute in those solutions is always approximately equal to the w/w% of that same solute in those same solutions. Applicants hope that this clarifies the arguments presented in the previous Office Action and Applicants respectfully request that the current rejections of the claims be withdrawn. Applicants further assert that, if the Examiner is unsatisfied with the above explanation, the Examiner phone the undersigned to discuss what, if any, additional proof of the relative equality of w/w% and w/v% for the compositions of Dobie et al. need be provided.

II. New Claims

Applicants have added new claims 23-26 to the present application for reciting further aspects of the subject matter of the present application.

CONCLUSION:

Applicants respectfully request reconsideration of the patentability of the claims of the present application. Should the Examiner have any questions regarding this Amendment, please feel free to contact the undersigned attorney at the phone number listed below.

Respectfully submitted,

ALCON RESEARCH, LTD.

December 13, 2011
Date

Scott A. Chapple, Agent
Reg. No. 46,287

Address for Correspondence:
Scott A. Chapple
Alcon Research, Ltd.
6201 S. Freeway, Mail Code TB4-8
Fort Worth, TX 76134-2099
Phone: 817-615-5288

Attorney Docket: 2667 US F

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Masood A. Chowhan et al.

U.S. Serial No.: 12/441,995

Confirmation No.: 7046

Filed: March 19, 2009

Examiner: Fay, Zohreh A.

Group Art Unit: 1627

CERTIFICATE OF FILING VIA EFS-WEB

I hereby certify that this correspondence is being submitted to the Mail Stop Amendment; Commissioner for Patents, P.O. Box 1450, Alexandria, VA. 22313-1450 via EFS-Web on this date:

December 13, 2011.

By: /Barbara McKenzie/
Barbara McKenzie

For: SELF PRESERVED AQUEOUS PHARMACEUTICAL COMPOSITIONS

THIRD SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT PURSUANT TO 37 C.F.R. 1.56, 1.97, AND 1.98

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Pursuant to the duty of disclosure under 37 C.F.R. § 1.97(c), Applicants submit the attached Form PTO/SB/08a. Neither a final Office Action under §1.113 nor a notice of allowance under §1.311 have been issued in the above-referenced application.

Because the PTO has waived the requirement under 37 CFR 1.98(a)(2) to submit copies of each cited U.S. patent and patent application publication in all U.S. national patent applications filed after June 30, 2003, none are enclosed. Only copies of cited foreign patent documents and non-patent literature are enclosed.

The requisite fee under 37 C.F.R. §1.17(p) has been charged to Deposit Account No. 010682 via EFS Web.

Applicants request that the listed references be considered during prosecution of this application, and that the references appear among the "References Cited" on any patent issuing herefrom.

Respectfully submitted,

December 13, 2011
Date

Scott A. Chapple
Registration No. 46,287

Address for Correspondence:
Alcon Research, Ltd.
Attn: Scott A. Chapple
6201 S. Freeway, TB4-8
Fort Worth, TX 76134-2099
Phone: 817-615-5288

Attorney Docket: 2667 US F

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	12441995
Filing Date	2009-03-19
First Named Inventor	Masood A. Chowhan
Art Unit	1627
Examiner Name	Fay, Zohreh A.
Attorney Docket Number	2667 US F

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Patent citation information please click the Add button. Add

U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20110195132		2011-08-11	Kabra et al.	

If you wish to add additional U.S. Published Application citation information please click the Add button. Add

FOREIGN PATENT DOCUMENTS Remove

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1							☐

If you wish to add additional Foreign Patent Document citation information please click the Add button Add

NON-PATENT LITERATURE DOCUMENTS Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	12441995
	Filing Date	2009-03-19
	First Named Inventor	Masood A. Chowhan
	Art Unit	1627
	Examiner Name	Fay, Zohreh A.
	Attorney Docket Number	2667 US F

	1		☐

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	12441995
	Filing Date	2009-03-19
	First Named Inventor	Masood A. Chowhan
	Art Unit	1627
	Examiner Name	Fay, Zohreh A.
	Attorney Docket Number	2667 US F

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☒ See attached certification statement.

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Scott A. Chapple, Reg. #46,287/	Date (YYYY-MM-DD)	2011-12-13
Name/Print	Scott A. Chapple	Registration Number	46,287

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Patent Application Fee Transmittal

Application Number:	12441995
Filing Date:	19-Mar-2009
Title of Invention:	SELF PRESERVED AQUEOUS PHARMACEUTICAL COMPOSITIONS
First Named Inventor/Applicant Name:	Masood A. Chowhan
Filer:	Scott Chapple/Barbara McKenzie
Attorney Docket Number:	2667 US F

Filed as Large Entity

U.S. National Stage under 35 USC 371 Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Claims in excess of 20	1615	4	60	240
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
		Total in USD ($)		**420**

Electronic Acknowledgement Receipt

EFS ID:	11606098
Application Number:	12441995
International Application Number:	
Confirmation Number:	7046
Title of Invention:	SELF PRESERVED AQUEOUS PHARMACEUTICAL COMPOSITIONS
First Named Inventor/Applicant Name:	Masood A. Chowhan
Customer Number:	26356
Filer:	Scott Chapple/Barbara McKenzie
Filer Authorized By:	Scott Chapple
Attorney Docket Number:	2667 US F
Receipt Date:	13-DEC-2011
Filing Date:	19-MAR-2009
Time Stamp:	15:21:13
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$420
RAM confirmation Number	1970
Deposit Account	010682
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. 1.492 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		2667_US_F_Amend_121311.pdf	374812 05131bf2e49a3f0f2b768ae3c7cb1d1049586f81	yes	9

Multipart Description/PDF files in .zip description

Document Description	Start	End
Amendment/Req. Reconsideration-After Non-Final Reject	1	1
Claims	2	4
Applicant Arguments/Remarks Made in an Amendment	5	9

Warnings:					
Information:					
2	Transmittal Letter	2667_US_F_IDS-S3_121311.pdf	72651 4d09a09deec146e09b5ef6684436fae0cb35e5f2	no	2
Warnings:					
Information:					
3	Information Disclosure Statement (IDS) Form (SB08)	2667_US_F_IDS-S3_sb08a_121311.pdf	612420 a47755b77c9016d3a2d0f0f0984a718089c60933	no	4
Warnings:					
Information:					
4	Fee Worksheet (SB06)	fee-info.pdf	32405 f00ed205b889f8a2b2dbe0fc43a70abd3b828c07	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	1092288		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 12/441,995	Filing Date 03/19/2009	☐ To be Mailed

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY ☐		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	12/13/2011	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 10	Minus	** 20	= 0	X $ =		OR	X $60=	0
	Independent (37 CFR 1.16(h))	* 2	Minus	***2	= 0	X $ =		OR	X $250=	0
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	0

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/PATRICIA WARNER/

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions and listings of claims in the application:

Claims 1-10 (canceled)

Claim 11 (previously presented): A multi-dose, self-preserved ophthalmic composition, said composition comprising:

a therapeutically effective amount of an ophthalmic therapeutic agent selected from the group consisting of beta-blockers, carbonic anhydrase inhibitors, prostaglandin analogs, neuroprotectants, anti-angiogenesis agents, quinolones, anti-inflammatory agents, growth factors, immunosuppressant agents and anti-allergic agents; and

a preservative system consisting essentially of:

i. borate at a concentration in the composition of 0.3 to 1.5 w/v% wherein the borate comprises one or more borates;

ii. polyol at a concentration in the composition of 0.6 to 2.0 w/v% wherein the polyol comprises sorbitol and propylene glycol; and

iii. zinc ions, wherein the zinc ions are provided by zinc chloride at a concentration in the composition of 0.0005 to 0.005 w/v %;

wherein the borate and polyol form a borate/polyol complex for enhancing the antimicrobial activity of the composition and wherein the preservative system has sufficient antimicrobial activity to allow the composition to satisfy USP 26 preservative efficacy requirements.

Claim 12 (canceled)

Claim 13 (canceled)

Claim 14 (previously presented): A composition as in claim 11 wherein the therapeutic agent is a prostaglandin analog.

Claim 15 (previously presented): A composition as in claim 11 wherein the therapeutic agent is travoprost.

Claim 16 (canceled)

Claim 17 (previously presented) A method of enhancing the antimicrobial activity of an aqueous ophthalmic pharmaceutical composition that, which comprises including a preservative system in the composition, the preservative system consisting essentially of:

i. borate at a concentration in the composition of 0.3 to 1.5 w/v% wherein the borate comprises one or more borates;
ii. polyol at a concentration in the composition of 0.6 to 2.0 w/v% wherein the polyol comprises sorbitol and propylene glycol; and
iii. zinc ions, wherein the zinc ions are provided by zinc chloride at a concentration in the composition of 0.0005 to 0.005 w/v %;

wherein:

i. the borate and polyol form a borate/polyol complex for enhancing the antimicrobial activity of the composition;
ii. the preservative system has sufficient antimicrobial activity to allow the composition to satisfy USP 26 preservative efficacy requirements; and
iii. the composition includes a therapeutically effective amount of an ophthalmic therapeutic agent selected from the group consisting of beta-blockers, carbonic anhydrase inhibitors, prostaglandin analogs, neuroprotectants, anti-angiogenesis agents, quinolones, anti-inflammatory agents, growth factors, immunosuppressant agents and anti-allergic agents.

Claim 18 (canceled)

Claim 19 (canceled)

Claim 20 (previously presented): A method as in claim 17 wherein the therapeutic agent is a prostaglandin analog.

Claim 21 (previously presented): A method as in claim 17 wherein the therapeutic agent is travoprost.

Claim 22 (canceled)

Claim 23 (new): A composition as in claim 11 wherein the concentration of borate in the composition is 0.5-1.2 w/v%.

Claim 24 (new): A composition as in claim 15 wherein the concentration of borate in the composition is 0.5-1.2 w/v%.

Claim 25 (new): A method as in claim 17 wherein the concentration of borate in the composition is 0.5-1.2 w/v%.

Claim 26 (new): A method as in claim 21 wherein the concentration of borate in the composition is 0.5-1.2 w/v%.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/441,995	03/19/2009	Masood A. Chowhan	2667 US F	7046

26356 7590 03/09/2012

ALCON
IP LEGAL, TB4-8
6201 SOUTH FREEWAY
FORT WORTH, TX 76134

EXAMINER	
FAY, ZOHREH A	

ART UNIT	PAPER NUMBER
1627	

MAIL DATE	DELIVERY MODE
03/09/2012	PAPER

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.

Office Action Summary	Application No.	Applicant(s)	
	12/441,995	CHOWHAN ET AL.	
	Examiner	Art Unit	
	ZOHREH FAY	1627	

-- 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 *13 December 2011*.

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) *11,14,15,17,20,21 and 23-26* 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) *11,14,15,17,20,21 and 23-26* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

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).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

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

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ 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) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/13/2011, 7/12/2011, 12/17/2010, 6/18/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Claims 11, 14, 15, 17, 20, 21 and 23-26 are presented for examination.

The amendments and remarks filed on December 13, 2011 have been received and entered.

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 negatived 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 1, 3-6 and 8-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chowhan et al. (2002/0123482) in view of WO Patent 2007/106723.

Chowhan et al. teach a multidose self- preserved ophthalmic composition comprising 0.5 to 6% borax/polyol complex and zinc ion in the form of Zinc chloride in combination with an active ingredient, such as amino acids. See Para [0013], Para [0020], Para [0021] and claims 15-16. The use of sorbitol and propylene glycol is taught in Para [0023]. Chowhan differs from the claimed invention in the concentrations of zinc chloride and specific active ingredients. The WO patent teaches the use of a Zinc-based preservative in an ophthalmic formulation with the improved safety and comfort. See page 1, lines 1-7. The concentrations encompassing the claimed concentrations are taught on page 7, lines 9-11. The use of therapeutic agents, such as anti-inflammatory agents and immunosuppressive agents are taught in page 9, lines 1-6. It would have been obvious to a person skilled in the art to use the claimed range concentrations for Zinc motivated by the teachings of WO Patent which teaches the use of such concentrations in ophthalmic formulations as old and well known. The motivation for adding the secondary components is also provided by WO Patent, which teaches the addition of the claimed active ingredients to a preserved zinc-based ophthalmic formulation as old and well known. Applicant's attention is again drawn to Chowhan Para [0013], which teaches the concentration range of 0.005 to about 0.015 mmol/l for zinc. Example 1 and claim16 of Chwohan also teach the concentration of 0.00015 for zinc, which is within the scope of what is claimed herein.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 11, 14, 15, 17, 20-21 and 23-26 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-18 of copending Application No. 13/ . Although the conflicting claims are not identical, they are not patentably distinct from each other because they overlap. The claims of the instant application are drawn to a mutidose self- preserved ophthalmic composition of a borate, a polyol and zinc ion and a method of enhancing the antimicrobial an ophthalmic composition. The claims of the copending application are drawn to a self-preserved ophthalmic composition of zinc, which further comprises a borate and polyol. The claims of the instant application are within the scope of the claims of the copending application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant's arguments and remarks have been carefully considered, but are not deemed to be persuasive. Applicant in his remarks argues the higher concentrations of zinc chloride, at least 2 fold higher of the WO patent in comparison with the lower concentrations of zinc claimed by the instant application. The arguments have been noted. It is the examiner's position that the WO patent on page 7 teaches a zinc compound at the claimed range concentrations. Applicant particularly refers to example 7 of the WO patent to show the higher concentration of zinc compound. It is the examiner's position that the concentrations in example 7 are cited as w/w, however, the concentrations of zinc in the instant claims are w/v. Applicant's attention is again drawn to Chowhan Para [0013], which teaches the concentration range of 0.005 to about

0.015 mmol/l for zinc. Example 1 and claim 16 of Chwohan also teach the concentration of 0.00015 for zinc, which is within the scope of what is claimed herein.

Applicant's submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on December 13, 2011 prompted the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 609.04(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ZOHREH FAY whose telephone number is (571)272-0573. The examiner can normally be reached on Monday to Friday 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni 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). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

ZF
/Zohreh A Fay/
Primary Examiner, Art Unit 1627

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	12441995
Filing Date	2009-03-19
First Named Inventor	Masood A. Chowhan
Art Unit	1627
Examiner Name	Fay, Zohreh A.
Attorney Docket Number	2667 US F

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	5460834		1995-10-24	Bhagat	

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Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20050214382		2005-09-29	Xia et al.	
	2	20070212420		2007-09-13	Xia et al.	
	3	20070297990		2007-12-27	Shah et al.	
	4	20100227003		2010-09-09	Shah et al.	

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Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	GUTTMAN, "Liquid gel therapy broadens role of dry eye product line", Ophthalmologytimes.com, 2006, pgs 33-34 and copyright notice	☐
	2	~~Illustration of packaging for Systane® free~~	☐

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Examiner Signature	/Zohreh Fay/ (03/08/2012)	Date Considered	

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[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20110195132		2011-08-11	Kabra et al.	

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Examiner Signature	/Zohreh Fay/ (02/24/2012)	Date Considered	

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	Attorney Docket Number	2667 US F

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☒ See attached certification statement.

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Scott A. Chapple, Reg. #46,287/	Date (YYYY-MM-DD)	2011-12-13
Name/Print	Scott A. Chapple	Registration Number	46,287

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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Art Unit	1627
Examiner Name	Fay, Zohreh A.
Attorney Docket Number	2667 US F

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Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	5130298		1992-07-14	Cini et al.	
	2	5820822		1998-10-13	Kross	
	3	7074827		2006-07-11	Ueno	
	4	7445771		2008-11-04	Dassanayake et al.	

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	1	20060205725		2006-09-14	Ueno	
	2	20080075790		2008-03-27	Kabra et al.	

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	1	98/10773	WO		1998-03-19	Richter Gedeon Vegyészeti		☐
	2	2007/106723	WO		2007-09-20	Bausch & Lomb Incorporated		☐
	3	2008/036847	WO		2008-03-27	Alcon Manufacturing, Ltd.		☐

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	1	Bruce Grahn et al., "Zinc and the Eye", JOURNAL OF THE AMERICAN COLLEGE OF NUTRITION, 106-118, 4-2001	☐

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EXAMINER SIGNATURE

Examiner Signature	/Zohreh Fay/ (02/21/2012)	Date Considered	

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Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12441995	CHOWHAN ET AL.
	Examiner	Art Unit
	ZOHREH A FAY	1612

SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
West	6/19/2010	ZF
Inventor search	6/19/2010	ZF
updated	3/9/2011	ZF
updated	7/28/2011	ZF
Updated	2/21/2012	ZF

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner

PTO/SB/08a (06-09)
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	1	4522806		1985-06-11	Muhlemann et al.	
	2	5221664		1993-06-22	Berkowitz et al.	
	3	5320843		1994-06-14	Raheja et al.	
	4	5352708		1994-10-04	Woodward et al.	
	5	5424078		1995-06-13	Dziabo et al.	
	6	5597559		1997-01-28	Olejnik et al.	
	7	5607698		1997-03-04	Martin et al.	
	8	5683993		1997-11-04	Tsao	

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	9	5725887		1998-03-10	Martin et al.	
	10	5736165		1998-04-07	Ripley et al.	
	11	5741817		1998-04-21	Chowhan et al.	
	12	5817277		1998-10-06	Mowrey-McKee et al.	
	13	5858346		1999-01-12	Vehige et al.	
	14	5858996		1999-01-12	Tsao	
	15	6017861		2000-01-25	Fujiwara et al.	
	16	6024954		2000-02-15	Park et al.	
	17	6034043		2000-03-07	Fujiwara et al.	
	18	6121315		2000-09-19	Nair et al.	
	19	6143799		2000-11-07	Chowhan et al.	

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	Application Number	12441995
	Filing Date	2009-03-19
	First Named Inventor	Masood A. Chowhan
	Art Unit	
	Examiner Name	
	Attorney Docket Number	2667 US F

	20	6319464		2001-11-20	Asgharian	
	21	6348190		2002-02-19	Illes et al.	
	22	6482799		2002-11-19	Tuse et al.	
	23	6492361		2002-12-10	Muller et al.	
	24	6503497		2003-01-07	Chowhan et al.	
	25	6583124		2003-06-24	Asgharian	

If you wish to add additional U.S. Patent citation information please click the Add button. Add

U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20020122831		2002-09-05	Mowrey-McKee et al.	
	2	20020123482		2002-09-05	Chowhan et al.	
	3	20050129771		2005-06-16	Asgharian	

If you wish to add additional U.S. Published Application citation information please click the Add button. Add

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /ZF/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	12441995
Filing Date	2009-03-19
First Named Inventor	Masood A. Chowhan
Art Unit	
Examiner Name	
Attorney Docket Number	2667 US F

FOREIGN PATENT DOCUMENTS Remove

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	2003-104870	JP		2003-04-09	Rohto Pharmaceutical Co., Ltd. / Kiyobashi		☒
	2	95/13050	WO		1995-05-18	Ciba-Geigy AG		☐
	3	2005/097067	WO		2005-10-20	Bausch & Lomb Incorporated		☐
	4	2008/042619	WO		2008-04-10	Alcon Manufacturing, Ltd.		☐

If you wish to add additional Foreign Patent Document citation information please click the Add button Add

NON-PATENT LITERATURE DOCUMENTS Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	Kabara, et al., Preservative-Free and Self-Preserving Cosmetics and Drugs – Principles and Practice, Chapter 1, pages 1-14, Marcel Dekker, Inc., 1997	☐
	2	McCarthy, "Metal Ions and Microbial Inhibitors", Cosmetic & Toiletries, 100:69-72, 1985	☐
	3	McCarthy, et al., "The Effect of Zinc Ions on the Antimicrobial Activity of Selected Preservatives", Journal of Pharmacy and Pharmacology, Vol. 41 (1989)	☐
	4	PCT International Preliminary Report On Patentability for corresponding application PCT/US2007/079094 with mailing date December 11, 2008	☐

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /ZF/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	12441995
	Filing Date	2009-03-19
	First Named Inventor	Masood A. Chowhan
	Art Unit	
	Examiner Name	
	Attorney Docket Number	2667 US F

	5	PCT International Search Report for corresponding application PCT/US2007/079094 with mailing date April 2, 2008	☐
	6	PCT Written Opinion for corresponding application PCT/US2007/079094 with mailing date April 2, 2008	☐
	7	Zeelie, et al., "Effects of Copper and Zinc Ions on the Germicidal Properties of Two Popular Pharmaceutical Antiseptic Agents, Cetylpyridinium Chloride and Povidone-iodine", Analyst, 123:503-507 (March 1998)	☐
	8	Zeelie, et al., "The Effects of Selected Metal Salts on the Microbial Activities of Agents used in the Pharmaceutical and Related Industries", Metal Compounds in Environment and Life, 4:193-200 (1992)	☐

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature	/Zohreh Fay/ (02/21/2012)	Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /ZF/

UNITED STATES PATENT AND TRADEMARK OFFICE

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United States Patent and Trademark Office
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P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/441,995	03/19/2009	Masood A. Chowhan	2667 US F	7046

26356 7590 05/24/2012

ALCON
IP LEGAL, TB4-8
6201 SOUTH FREEWAY
FORT WORTH, TX 76134

EXAMINER	
FAY, ZOHREH A	

ART UNIT	PAPER NUMBER
1627	

MAIL DATE	DELIVERY MODE
05/24/2012	PAPER

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.

Applicant-Initiated Interview Summary	Application No.	Applicant(s)	
	12/441,995	CHOWHAN ET AL.	
	Examiner	Art Unit	
	ZOHREH FAY	1627	

All participants (applicant, applicant's representative, PTO personnel):

(1) *ZOHREH FAY*.

(3) *Scott Chapple*.

(2) *Patrick Ryan*.

(4)_____.

Date of Interview: *22 May 2012*.

Type: ☐ Telephonic ☐ Video Conference
☒ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☐ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☐102 ☒103 ☐Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: *all*.

Identification of prior art discussed: *all*.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

The obviousness rejection was discussed. Applicant will consider submitting arguments and/or data to overcome the obviousness rejection.

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/Zohreh A Fay/ Primary Examiner, Art Unit 1627	

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews
Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

UNITED STATES PATENT AND TRADEMARK OFFICE

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www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/441,995	03/19/2009	Masood A. Chowhan	2667 US F	7046

26356 7590 05/30/2012

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6201 SOUTH FREEWAY
FORT WORTH, TX 76134

EXAMINER	
FAY, ZOHREH A	

ART UNIT	PAPER NUMBER
1627	

MAIL DATE	DELIVERY MODE
05/30/2012	PAPER

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.

Interview Summary	Application No.	Applicant(s)	
	12/441,995	CHOWHAN ET AL.	
	Examiner	Art Unit	
	ZOHREH FAY	1627	

All participants (applicant, applicant's representative, PTO personnel):

(1) *ZOHREH FAY*. (3)_____.

(2) *Scott Chapple*. (4)_____.

Date of Interview: *10 May 2011*.

Type: a)☐ Telephonic b)☐ Video Conference
c)☒ Personal [copy given to: 1)☐ applicant 2)☐ applicant's representative]

Exhibit shown or demonstration conducted: d)☐ Yes e)☒ No.
If Yes, brief description: _____.

Claim(s) discussed: *All*.

Identification of prior art discussed: *All*.

Agreement with respect to the claims f)☐ was reached. g)☐ was not reached. h)☒ N/A.

Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: *Applicant argued the lowest level of zinc, which passes efficacey standards.*.

(A fuller description, if necessary, and a copy of the amendments which the examiner agreed would render the claims allowable, if available, must be attached. Also, where no copy of the amendments that would render the claims allowable is available, a summary thereof must be attached.)

THE FORMAL WRITTEN REPLY TO THE LAST OFFICE ACTION MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a reply to the last Office action has already been filed, APPLICANT IS GIVEN A NON-EXTENDABLE PERIOD OF THE LONGER OF ONE MONTH OR THIRTY DAYS FROM THIS INTERVIEW DATE, OR THE MAILING DATE OF THIS INTERVIEW SUMMARY FORM, WHICHEVER IS LATER, TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW. See Summary of Record of Interview requirements on reverse side or on attached sheet.

/Zohreh A Fay/ Primary Examiner, Art Unit 1627	

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
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- Name of applicant
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- Date of interview
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- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
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2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Masood A. Chowhan et al.

U.S. Serial No.: 12/441,995

Confirmation No.: 7046

Filed: March 19, 2009

Examiner: Fay, Zohreh A.

Group Art Unit: 1627

For: SELF PRESERVED AQUEOUS PHARMACEUTICAL COMPOSITIONS

CERTIFICATE OF FILING VIA EFS-WEB

I hereby certify that this correspondence is being submitted to the Mail Stop AF; Commissioner for Patents, P.O. Box 1450, Alexandria, VA. 22313-1450 via EFS-Web on this date:

June 15, 2012.

By: /Barbara McKenzie/
Barbara McKenzie

RESPONSE AFTER FINAL

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir or Madam:

This paper is submitted in response to the Final Office Action dated March 9, 2012, for which the Examiner has set a three-month period for response.

With this Response, Applicants have submitted a request for a one-month extension of time. If the U.S. Patent Office deems any fees to be deficient or absent, consider this paragraph a request and authorization to deduct said fees from Alcon Research, Ltd. Deposit Account No. 010682.

Reconsideration of the application is respectfully requested.

A listing of claims begins on page 2 of this paper.

Remarks begin on page 5 of this paper.

REMARKS

Applicants thank Examiner Fay for the courtesies granted during the Interview conducted on May 22, 2012. During the interview, the obviousness rejection and an experiment to address it were discussed. Applicants have now conducted an experiment, necessitating the requested one-month extension of time, and now submit this response, along with an IDS submission, as discussed during the interview and in view of the AFCP program.

The Final Office Action rejects Claims 1, 3 – 6, and 8 – 10 under 35 USC 103(a) as unpatentable over Chowhan et al. (2002/0123482) in view of WO Patent (2007/106723) and Claims 11, 14, 15, 17, 20, 21, and 23 – 26 under an obviousness-type double patenting.

I. Rejection under 35 USC 103

The present Office Action rejects Claims 1, 3 – 6, and 8 - 10. Of course, these claims were previously canceled and are no longer pending in the present application. As such, this rejection was made in error. During the Interview, Applicants discussed this error with Examiner Fay and discussed the best course of action for responding to the current Office Action. Accordingly, Applicants would not need to request the issuance of a new (corrected/replacement) Office Action.

To the extent that the obviousness rejection may apply to the pending claims (Claims 11, 14, 17, 20, 21, and 23 – 26), Applicants submit the following response. During the Interview, Examiner Fay suggested that her hesitation in allowing the claims of the present application was rooted in Example 1 of US 2002/0123482 to Chowhan et al. It was understood that the "consisting essentially of" language in the claims of the present application limited the preservative system to a system including substantially only the borate, the polyol and the zinc as specified in claims, and that conventional preservative ingredients (such as benzalkonium chloride or polyquaternium-1) were excluded. Indeed, the Specification makes it clear that the compositions of the present invention do not require a convention antimicrobial preservative (see, for example, page 5, lines 9 – 11; page 5 , line 29 – page 6, line 3; page 6, lines 17 – 20; and

page 9, lines 7 – 11) in order to meet USP preservative efficacy requirements, Applicants' pending claims recite a composition comprising a preservative system that consists essentially of recited borate, polyol and zinc components. As Applicants emphasized in the Interview, the presence of a conventional preservative would materially affect the nature of the presently claimed invention.

Additionally, Examiner Fay suggested that it had not been shown that the polyquaternium-1 in composition of Example 1 of Chowhan et al. had a material effect on the preservation efficacy of that composition. It was agreed that a showing of such a material effect would favor the patentability of the claims of the application. In particular, it was agreed that Applicants should perform preservation efficacy testing on a composition substantially identical to the composition of Example 1 of Chowhan et al., with the exception that polyquaternium-1 should be removed from the reference composition and the concentration of zinc should be elevated to 0.015 mmol/L (i.e., 0.00021% w/v), which is the upper limit provided in paragraph [0013] of Chowhan et al.

Applicants performed this testing and the results are provided in a declaration under 37 C.F.R. §1.132, which is included herewith. This declaration clearly establishes that removal of polyquaternium-1 from the composition of Example 1 of Chowhan et al. causes that composition to fail USP 24 Preservation Efficacy. In contrast to this, the composition of Example 1 of Chowhan et al. (i.e., with polyquaternium-1 present) passes USP 24 preservation efficacy testing requirements (see results shown in Example 3 of Chowhan et al.). Thus, the polyquaternium-1 in the composition of Example 1 of Chowhan et al. is clearly essential to its ability to satisfy preservation efficacy requirements.

In view of the above, Applicants respectfully request reconsideration of the rejections of the claims of the present application and respectfully request that the present application be given a Notice of Allowance.

II. Obviousness-Type Double Patenting

The Office Action rejected the currently pending claims (Claims 11, 14, 15, 17, 20, 21, and 23 – 26) for obviousness-type double patenting. However, the Office Action did not make clear which references were being used to reject the claims. During a teleconference with Examiner Fay on March 27, 2012, Applicants clarified that the obviousness-type double patenting rejections in the Office Action were made relative to U.S. Patent Application Serial No. 11/858,781 and U.S. Patent Application Serial No. 13/086,950. In response, Applicants submits herewith terminal disclaimers to overcome those rejections.

III. Information Disclosure Statement

Although the "Illustration of Packaging for Systane® Free" item was apparently considered by the Examiner according to the IDS attached to the Office Action dated 9/16/2011 (which was signed by the Examiner on 7/28/2011), the IDS attached to the instant Final Office Action (which was signed by the Examiner on 3/8/2012) indicates that the Examiner did not consider this reference. Applicants understood that the Examiner lined through this reference on the IDS attached to the Office Action because no date for this reference was included in the IDS form. During the Interview, Applicants explained that the illustration was merely the packaging of the product and that this product was fully described in the Information Disclosure Statement filed on July 12, 2011. Applicants further explained that the GUTTMAN reference (Liquid gel therapy broadens role of dry eye product line, Ophthalmologytimes.com, 2006, pgs 33-34), which includes a description of the Systane® Free product, was already considered. In view of this information, it was agreed that Applicants should submit an Information Disclosure Statement that included the Illustration of packaging for the Systane® Free artificial tear product, indicating a date on the IDS, as well as two other references related to the same product, and that Examiner Fay would consider these references after final rejection as long as they did not raise any substantial new issues.

CONCLUSION:

Applicants respectfully request allowance of the pending claims of the present application in view of the above remarks. Should the Examiner have any questions regarding this Amendment, please feel free to contact the undersigned attorney at the phone number listed below.

Respectfully submitted,

ALCON RESEARCH, LTD.

June 15, 2012
Date

Scott A. Chapple, Agent
Reg. No. 46,287

Address for Correspondence:
Alcon Research, Ltd.
Scott A. Chapple, IP Legal
6201 S. Freeway, Mail Code TB4-8
Fort Worth, TX 76134-2099
Phone: 817-615-5288

Attorney Docket: 2667 US F

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Masood A. Chowhan et al.

U.S. Serial No.: 12/441,995

Confirmation No.: 7046

Filed: March 19, 2009

Examiner: Fay, Zohreh A.

Group Art Unit: 1627

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I hereby certify that this correspondence is being submitted to the Mail Stop Amendment; Commissioner for Patents, P.O. Box 1450, Alexandria, VA. 22313-1450 via EFS-Web on this date:

June 15, 2012.

By: /Barbara McKenzie/
Barbara McKenzie

For: SELF PRESERVED AQUEOUS PHARMACEUTICAL COMPOSITIONS

DECLARATION UNDER 37 CFR §1.132

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, Bhagwati Kabra, hereby say and declare as follows.

1. I received my B.S. in Chemical Engineering (B.S.Ch.E) from the Bombay University, Department of Chemical Technology in 1982, M.S. in Chemical Engineering from the University of Cincinnati, in 1989 and Ph.D. in Chemical Engineering from the University of Cincinnati, in 1993. Since 1993, I have worked at Alcon Research, Ltd. or its predecessors ("Alcon"), where I have held positions of increasing responsibility in the Pharmaceutical Sciences Group starting from a senior scientist I in drug delivery to a manager in the formulation development group to director of confirmatory chemistry manufacturing controls (CMC) teams.

2. As Director of CMC teams for confirmatory projects at Alcon, my responsibilities include leading, managing and instructing multiple CMC teams that comprise a formulation scientist, a development chemist and a process engineer and other ad-hoc members.

3. My pharmaceutical product research and development experience has been continuous since 1993 at Alcon where I have worked on different dosage forms and compositions for ophthalmic compositions and other pharmaceutical compositions.

4. At the request of attorney Scott Chapple, I instructed one of the formulation scientists at Alcon to prepare the following formulation shown in Table A:

TABLE A

Ingredients	Formula 1
Sodium Chloride	0.4% w/v
Potassium Chloride	0.038% w/v
Magnesium Chloride, Hexahydrate	0.0065% w/v
Calcium Chloride, Dihydrate	0.0053% w/v
Zinc Chloride	0.00021% w/v
Glycine	0.1% w/v
Boric Acid	0.8% w/v
Polysorbate 80	0.005% w/v
Glycerin	0.2% w/v
Dextran 70	0.1% w/v
HPMC (2910 E4M)	0.3% w/v
Sodium Hydroxide	pH Adjust to 7.4
Hydrochloric Acid	pH Adjust to 7.4
Purified Water	qs to 100%

5. Also at the request of attorney Scott Chapple, I requested the microbiology group at Alcon to perform a preservation efficacy study on the

formulation according to the United States Pharmacopeia 24th edition protocol. The results are provided below in Table B:

TABLE B

Formula 1	Day 7	PET Result
S. aureus	0.9	Fail
P. aeruginosa	0.2	Fail
E. coli	0.0	Fail

6. The numbers in Table B in the column labeled Day 7 represent log reductions achieved during testing of the following three bacteria: Staphylococcus Aureus, Pseudomonas Aeruginosa and Escheria Coli. To pass the USP 24 preservation efficacy tests, a composition must exhibit at least a 1.0 log reduction in each of these three bacteria by day 7. As can be seen, the composition of Table A fails to show such a reduction for any of the three bacteria. Thus, the tested composition fails USP 24 preservation efficacy requirements.

7. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine, imprisonment, or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing therefrom.

Date: June 15, 2012

Bhagwati Kabra

Bhagwati Kabra, Ph.D.

PTO/SB/25 (08-11)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

TERMINAL DISCLAIMER TO OBVIATE A PROVISIONAL DOUBLE PATENTING REJECTION OVER A PENDING "REFERENCE" APPLICATION

Docket Number (Optional): 2667 US F

In re Application of: Masood A. Chowhan et al.

Application No.: 12/441,995

Filed: March 19, 2009

For: Self-Preserved Aqueous Pharmaceutical Compositions

The owner*, Alcon Research, Ltd., of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of any patent granted on pending **reference** Application Number 11/858,781, filed September 20, 2007, as the term of any patent granted on said **reference** application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending **reference** application. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and any patent granted on the **reference** application are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term of any patent granted on said **reference** application, "as the term of any patent granted on said **reference** application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending **reference** application," in the event that: any such patent: granted on the pending **reference** application: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321, has all claims canceled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as shortened by any terminal disclaimer filed prior to its grant.

Check either box 1 or 2 below, if appropriate.

1. ☐ For submissions on behalf of a business/organization (e.g., corporation, partnership, university, government agency, etc.), the undersigned is empowered to act on behalf of the business/organization.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

2. ☑ The undersigned is an attorney or agent of record. Reg. No. 46,287

Signature — Date: 15 June 2012

Scott A. Chapple
Typed or printed name

817-615-5288
Telephone Number

☑ Terminal disclaimer fee under 37 CFR 1.20(d) is included.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

*Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner). Form PTO/SB/96 may be used for making this statement. See MPEP § 324.

PTO/SB/96 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: Alcon Research, Ltd.

Application No./Patent No.: 11/858,781 Filed/Issue Date: September 20, 2007

Titled: Self-Preserved Aqueous Pharmaceutical Compositions

Alcon Research, Ltd. , a corporation

(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.

states that it is:

1. [X] the assignee of the entire right, title, and interest in;

2. [ ] an assignee of less than the entire right, title, and interest in (The extent (by percentage) of its ownership interest is _____ %); or

3. [ ] the assignee of an undivided interest in the entirety of (a complete assignment from one of the joint inventors was made) the patent application/patent identified above, by virtue of either:

A. [ ] An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or for which a copy therefore is attached.

OR

B. [X] A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: Inventors To: Alcon Manufacturing, Ltd.

The document was recorded in the United States Patent and Trademark Office at Reel 019856, Frame 0532, or for which a copy thereof is attached.

2. From: Alcon Manufacturing, Ltd. To: Alcon Research, Ltd.

The document was recorded in the United States Patent and Trademark Office at Reel 021266, Frame 0729, or for which a copy thereof is attached.

3. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or for which a copy thereof is attached.

[ ] Additional documents in the chain of title are listed on a supplemental sheet(s).

[ ] As required by 37 CFR 3.73(b)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (*i.e.*, a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

Signature

15 June 2012
Date

Scott A. Chapple
Printed or Typed Name

Attorney/Agent of Record
Title

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	12441995
Filing Date	2009-03-19
First Named Inventor	Masood A. Chowhan
Art Unit	1627
Examiner Name	Fay, Zohreh A.
Attorney Docket Number	2667 US F

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Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
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	Filing Date	2009-03-19
	First Named Inventor	Masood A. Chowhan
	Art Unit	1627
	Examiner Name	Fay, Zohreh A.
	Attorney Docket Number	2667 US F

	1	HOFFMAN H.M. et al., "Pre-clinical in vitro Testing of an Artificial Tear Formulation with a Novel Preservation System", poster presentation at the annual meeting of the Association for Research In Vision And Ophthalmology (ARVO), Ft. Lauderdale, FL., April 30, 2006	☐
	2	Illustration of packaging for Systane® Free, March 7, 2006	☐
	3	SYSTANE® FREE promotional document (minimal-blur) published on or about January 1, 2006	☐

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EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	12441995
	Filing Date	2009-03-19
	First Named Inventor	Masood A. Chowhan
	Art Unit	1627
	Examiner Name	Fay, Zohreh A.
	Attorney Docket Number	2667 US F

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☒ See attached certification statement.

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Scott A. Chapple, Reg. #46,287/	Date (YYYY-MM-DD)	2012-06-15
Name/Print	Scott A. Chapple	Registration Number	46,287

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

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Electronic Patent Application Fee Transmittal

Application Number:	12441995
Filing Date:	19-Mar-2009
Title of Invention:	SELF PRESERVED AQUEOUS PHARMACEUTICAL COMPOSITIONS
First Named Inventor/Applicant Name:	Masood A. Chowhan
Filer:	Scott Chapple/Barbara McKenzie
Attorney Docket Number:	2667 US F

Filed as Large Entity

U.S. National Stage under 35 USC 371 Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
Statutory or terminal disclaimer	1814	2	160	320
		Total in USD ($)		**500**

Electronic Acknowledgement Receipt

EFS ID:	13030132
Application Number:	12441995
International Application Number:	
Confirmation Number:	7046
Title of Invention:	SELF PRESERVED AQUEOUS PHARMACEUTICAL COMPOSITIONS
First Named Inventor/Applicant Name:	Masood A. Chowhan
Customer Number:	26356
Filer:	Scott Chapple/Barbara McKenzie
Filer Authorized By:	Scott Chapple
Attorney Docket Number:	2667 US F
Receipt Date:	15-JUN-2012
Filing Date:	19-MAR-2009
Time Stamp:	16:57:22
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$500
RAM confirmation Number	4354
Deposit Account	010682
Authorized User	

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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		2667_US_F_Response_061512.pdf	355474 b28d3ea223ce7fef348dbce2c929eb9d08fb54e4	yes	8
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Amendment After Final		1	1	
	Claims		2	4	
	Applicant Arguments/Remarks Made in an Amendment		5	8	
Warnings:					
Information:					
2	Rule 130, 131 or 132 Affidavits	2667_US_F_132Decl_061512.pdf	135776 ea8c675e4552930737b7d0912e5508fddd2e7794	no	3
Warnings:					
Information:					
3	Terminal Disclaimer Filed	USSN_11-858781_sb25_061512.pdf	100184 a16f41da44dd7cbe85a567f1dd119895d7034881	no	1
Warnings:					
Information:					
4	Assignee showing of ownership per 37 CFR 3.73(b).	USSN_11-858781_sb96_061512.pdf	95552 5155e512a660b96690f4699698c068b39c5a9614	no	1
Warnings:					
Information:					
5	Terminal Disclaimer Filed	USSN_13-086950_sb25_061512.pdf	101022 bcdd4b4266a7a02e30ecfb8ee0a8f079f13abd8e	no	1
Warnings:					
Information:					
6	Assignee showing of ownership per 37 CFR 3.73(b).	USSN_13-086950_sb96_061512.pdf	95115 390eda167e412c8d41645763c558f754fa1cdccf	no	1
Warnings:					

Information:					
7	Transmittal Letter	2667_US_F_IDS-S4_061512.pdf	83511 0cef5c06c2dc0a239e581cddd2620f1356532682	no	2
Warnings:					
Information:					
8	Information Disclosure Statement (IDS) Form (SB08)	2667_US_F_IDS-S4_08a_061512.pdf	612701 a423ea5a7ebb14c51fa87744b721c0e0e06441d6	no	4
Warnings:					
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9	Non Patent Literature	Hoffman_et_al_2006-04-30.pdf	263962 70f7c59d27cbba45054ea327b8586fc267d03d65	no	1
Warnings:					
Information:					
10	Non Patent Literature	Systane_Free_Packaging.pdf	117195 904505e9423f466bbc071a7252b4a37b737d34f5	no	1
Warnings:					
Information:					
11	Non Patent Literature	Systane_Free_promotional_2006.pdf	202005 b426e99c7ccce7f1fa31f7e6c15f88e3164e09e2	no	2
Warnings:					
Information:					
12	Fee Worksheet (SB06)	fee-info.pdf	32163 a1182b243b2c41e5a47bf51af1c77f2f756c4a91	no	2
Warnings:					
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			Total Files Size (in bytes):	2194660	

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New International Application Filed with the USPTO as a Receiving Office

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PTO/SB/25 (08-11)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

TERMINAL DISCLAIMER TO OBVIATE A PROVISIONAL DOUBLE PATENTING REJECTION OVER A PENDING "REFERENCE" APPLICATION

Docket Number (Optional): 2667 US F

In re Application of: Masood A. Chowhan et al.

Application No.: 12/441,995

Filed: March 19, 2009

For: Self-Preserved Aqueous Pharmaceutical Compositions

The owner*, Alcon Research, Ltd., of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of any patent granted on pending **reference** Application Number 13/086950, filed April 14, 2011, as the term of any patent granted on said **reference** application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending **reference** application. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and any patent granted on the **reference** application are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

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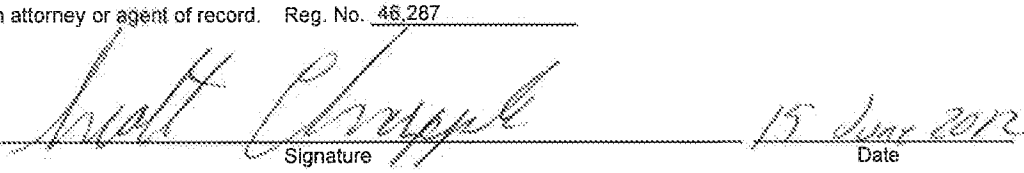
Check either box 1 or 2 below, if appropriate.

1. ☐ For submissions on behalf of a business/organization (e.g., corporation, partnership, university, government agency, etc.), the undersigned is empowered to act on behalf of the business/organization.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

2. ☑ The undersigned is an attorney or agent of record. Reg. No. 46,287



Signature — 15 Jun 2012 — Date

Scott A. Chapple
Typed or printed name

817-615-5288
Telephone Number

☑ Terminal disclaimer fee under 37 CFR 1.20(d) is included.

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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: Alcon Research, Ltd.

Application No./Patent No.: 13/086,950 Filed/Issue Date: April 14, 2011

Titled: Self-Preserved Aqueous Pharmaceutical Compositions

Alcon Research, Ltd., a corporation

(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.

states that it is:

1. [X] the assignee of the entire right, title, and interest in;

2. [ ] an assignee of less than the entire right, title, and interest in (The extent (by percentage) of its ownership interest is _____ %); or

3. [ ] the assignee of an undivided interest in the entirety of (a complete assignment from one of the joint inventors was made) the patent application/patent identified above, by virtue of either:

A. [ ] An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or for which a copy therefore is attached.

OR

B. [X] A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: Inventors To: Alcon Manufacturing, Ltd.

The document was recorded in the United States Patent and Trademark Office at
Reel 019856, Frame 0532, or for which a copy thereof is attached.

2. From: Alcon Manufacturing, Ltd. To: Alcon Research, Ltd.

The document was recorded in the United States Patent and Trademark Office at
Reel 021266, Frame 0729, or for which a copy thereof is attached.

3. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

[ ] Additional documents in the chain of title are listed on a supplemental sheet(s).

[ ] As required by 37 CFR 3.73(b)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (*i.e.*, a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

Signature

15 June 2012
Date

Scott A. Chapple
Printed or Typed Name

Attorney/Agent of Record
Title

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Masood A. Chowhan et al.

U.S. Serial No.: 12/441,995

Confirmation No.: 7046

Filed: March 19, 2009

Examiner: Fay, Zohreh A.

Group Art Unit: 1627

For: SELF PRESERVED AQUEOUS PHARMACEUTICAL COMPOSITIONS

FOURTH SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT PURSUANT TO 37 C.F.R. 1.56, 1.97(c), AND 1.98

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Pursuant to the duty of disclosure under 37 C.F.R. § 1.97(c), Applicants submit the attached PTO Form PTO/SB/08a. Neither a final Office Action under §1.113 nor a notice of allowance under §1.311 have been issued in the above-referenced application.

This Information Disclosure Statement cites three references. Each of the three references relates to Systane® Free, an artificial tear product marketed by the assignee of the present application. The composition of Systane® Free was disclosed in detail in the Information Disclosure Statement that was filed in present application on July 12, 2011.

Because the PTO has waived the requirement under 37 CFR 1.98(a)(2) to submit copies of each cited U.S. patent and patent application publication in all U.S. national patent applications filed after June 30, 2003, none are enclosed. Only copies of cited foreign patent documents and non-patent literature are enclosed.

Applicants request that the listed references be considered during prosecution of this application, and that the references appear among the "References Cited" on any patent issuing herefrom.

The requisite fee under 37 C.F.R. §1.17(p) has been charged to Deposit Account No. 010682 via EFS Web.

Respectfully submitted,

June 15, 2012
Date

Scott A. Chapple
Registration No. 46,287

Address for Correspondence:
Alcon Research, Ltd.
Attn: Scott A. Chapple
6201 S. Freeway, TB4-8
Fort Worth, TX 76134-2099
Phone: 817-615-5288

Attorney Docket: 2667 US F

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 12/441,995	Filing Date 03/19/2009	☐ To be Mailed

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY ☐		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	06/15/2012	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 10	Minus	** 20	= 0	X $ =		OR	X $60=	0
	Independent (37 CFR 1.16(h))	* 2	Minus	***3	= 0	X $ =		OR	X $250=	0
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	0

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/Tina J. Barden/

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Document code: WFEE

United States Patent and Trademark Office
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01 FC : 1251 150.00 DA

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions and listings of claims in the application:

Claims 1-10 (canceled)

Claim 11 (previously presented): A multi-dose, self-preserved ophthalmic composition, said composition comprising:

a therapeutically effective amount of an ophthalmic therapeutic agent selected from the group consisting of beta-blockers, carbonic anhydrase inhibitors, prostaglandin analogs, neuroprotectants, anti-angiogenesis agents, quinolones, anti-inflammatory agents, growth factors, immunosuppressant agents and anti-allergic agents; and

a preservative system consisting essentially of:

i. borate at a concentration in the composition of 0.3 to 1.5 w/v% wherein the borate comprises one or more borates;

ii. polyol at a concentration in the composition of 0.6 to 2.0 w/v% wherein the polyol comprises sorbitol and propylene glycol; and

iii. zinc ions, wherein the zinc ions are provided by zinc chloride at a concentration in the composition of 0.0005 to 0.005 w/v %;

wherein the borate and polyol form a borate/polyol complex for enhancing the antimicrobial activity of the composition and wherein the preservative system has sufficient antimicrobial activity to allow the composition to satisfy USP 26 preservative efficacy requirements.

Claim 12 (canceled)

Claim 13 (canceled)

Claim 14 (previously presented): A composition as in claim 11 wherein the therapeutic agent is a prostaglandin analog.

Claim 15 (previously presented): A composition as in claim 11 wherein the therapeutic agent is travoprost.

Claim 16 (canceled)

Claim 17 (previously presented) A method of enhancing the antimicrobial activity of an aqueous ophthalmic pharmaceutical composition that, which comprises including a preservative system in the composition, the preservative system consisting essentially of:

i. borate at a concentration in the composition of 0.3 to 1.5 w/v% wherein the borate comprises one or more borates;
ii. polyol at a concentration in the composition of 0.6 to 2.0 w/v% wherein the polyol comprises sorbitol and propylene glycol; and
iii. zinc ions, wherein the zinc ions are provided by zinc chloride at a concentration in the composition of 0.0005 to 0.005 w/v %;

wherein:

i. the borate and polyol form a borate/polyol complex for enhancing the antimicrobial activity of the composition;
ii. the preservative system has sufficient antimicrobial activity to allow the composition to satisfy USP 26 preservative efficacy requirements; and
iii. the composition includes a therapeutically effective amount of an ophthalmic therapeutic agent selected from the group consisting of beta-blockers, carbonic anhydrase inhibitors, prostaglandin analogs, neuroprotectants, anti-angiogenesis agents, quinolones, anti-inflammatory agents, growth factors, immunosuppressant agents and anti-allergic agents.

Claim 18 (canceled)

Claim 19 (canceled)

Claim 20 (previously presented): A method as in claim 17 wherein the therapeutic agent is a prostaglandin analog.

Claim 21 (previously presented): A method as in claim 17 wherein the therapeutic agent is travoprost.

Claim 22 (canceled)

Claim 23 (previously presented): A composition as in claim 11 wherein the concentration of borate in the composition is 0.5-1.2 w/v%.

Claim 24 (previously presented): A composition as in claim 15 wherein the concentration of borate in the composition is 0.5-1.2 w/v%.

Claim 25 (previously presented): A method as in claim 17 wherein the concentration of borate in the composition is 0.5-1.2 w/v%.

Claim 26 (previously presented): A method as in claim 21 wherein the concentration of borate in the composition is 0.5-1.2 w/v%.

Application Number	Application/Control No.	Applicant(s)/Patent under Reexamination	
	12/441,995	CHOWHAN ET AL.	

Document Code - DISQ	Internal Document – DO NOT MAIL

TERMINAL DISCLAIMER	☒ APPROVED	☐ DISAPPROVED
Date Filed : 6/15/12	This patent is subject to a Terminal Disclaimer	

Approved/Disapproved by:

ANDRE ROBINSON

2 TDS WERE APPRVD.

U.S. Patent and Trademark Office

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

26356 7590 08/28/2012

ALCON
IP LEGAL, TB4-8
6201 SOUTH FREEWAY
FORT WORTH, TX 76134

EXAMINER
FAY, ZOHREH A

ART UNIT	PAPER NUMBER
1627	

DATE MAILED: 08/28/2012

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/441,995	03/19/2009	Masood A. Chowhan	2667 US F	7046

TITLE OF INVENTION: SELF PRESERVED AQUEOUS PHARMACEUTICAL COMPOSITIONS

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1740	$300	$0	$2040	11/28/2012

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

B. If the status above is to be removed, check box 5b on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above, or

If the SMALL ENTITY is shown as NO:

A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check box 5a on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and 1/2 the ISSUE FEE shown above.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

26356 7590 08/28/2012

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FORT WORTH, TX 76134

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/441,995	03/19/2009	Masood A. Chowhan	2667 US F	7046

TITLE OF INVENTION: SELF PRESERVED AQUEOUS PHARMACEUTICAL COMPOSITIONS

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1740	$300	$0	$2040	11/28/2012

EXAMINER	ART UNIT	CLASS-SUBCLASS
FAY, ZOHREH A	1627	424-078040

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,

(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____

2 _____

3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:

❑ Issue Fee

❑ Publication Fee (No small entity discount permitted)

❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**

❑ A check is enclosed.

❑ Payment by credit card. Form PTO-2038 is attached.

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

❑ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.

❑ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PTOL-85 (Rev. 02/11) Approved for use through 08/31/2013. OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/441,995	03/19/2009	Masood A. Chowhan	2667 US F	7046

26356 7590 08/28/2012

ALCON
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6201 SOUTH FREEWAY
FORT WORTH, TX 76134

EXAMINER	
FAY, ZOHREH A	

ART UNIT	PAPER NUMBER
1627	

DATE MAILED: 08/28/2012

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)

(application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 0 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 0 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No.	Applicant(s)	
	12/441,995	CHOWHAN ET AL.	
	Examiner	Art Unit	
	ZOHREH FAY	1627	

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

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *the amendments and declaration filed on 6/15/2012*.
2. ☐ 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.
3. ☒ The allowed claim(s) is/are *11,14,15,17,20,21 and 24-26*.
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ 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)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.
6. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
7. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date See Continuation Sheet
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application
6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
7. ☐ Examiner's Amendment/Comment
8. ☐ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

/Zohreh A Fay/
Primary Examiner, Art Unit 1627

Continuation of Attachment(s) 3. Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date: 6/18/2009, 12/17/2010, 7/12/2011, 12/13/2011, 6/15/2012.

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	12441995
Filing Date	2009-03-19
First Named Inventor	Masood A. Chowhan
Art Unit	1627
Examiner Name	Fay, Zohreh A.
Attorney Docket Number	2667 US F

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Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /ZF/

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	Attorney Docket Number	2667 US F

	1	HOFFMAN H.M. et al., "Pre-clinical in vitro Testing of an Artificial Tear Formulation with a Novel Preservation System", poster presentation at the annual meeting of the Association for Research In Vision And Ophthalmology (ARVO), Ft. Lauderdale, FL., April 30, 2006	☐
	2	Illustration of packaging for Systane® Free, March 7, 2006	☐
	3	SYSTANE® FREE promotional document (minimal-blur) published on or about January 1, 2006	☐

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EXAMINER SIGNATURE

Examiner Signature	/Zohreh Fay/ (07/01/2012)	Date Considered	

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CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☒ See attached certification statement.

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Scott A. Chapple, Reg. #46,287/	Date (YYYY-MM-DD)	2012-06-15
Name/Print	Scott A. Chapple	Registration Number	46,287

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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First Named Inventor	Masood A. Chowhan
Art Unit	
Examiner Name	
Attorney Docket Number	2667 US F

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Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	4522806		1985-06-11	Muhlemann et al.	
	2	5221664		1993-06-22	Berkowitz et al.	
	3	5320843		1994-06-14	Raheja et al.	
	4	5352708		1994-10-04	Woodward et al.	
	5	5424078		1995-06-13	Dziabo et al.	
	6	5597559		1997-01-28	Olejnik et al.	
	7	5607698		1997-03-04	Martin et al.	
	8	5683993		1997-11-04	Tsao	

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	9	5725887		1998-03-10	Martin et al.	
	10	5736165		1998-04-07	Ripley et al.	
	11	5741817		1998-04-21	Chowhan et al.	
	12	5817277		1998-10-06	Mowrey-McKee et al.	
	13	5858346		1999-01-12	Vehige et al.	
	14	5858996		1999-01-12	Tsao	
	15	6017861		2000-01-25	Fujiwara et al.	
	16	6024954		2000-02-15	Park et al.	
	17	6034043		2000-03-07	Fujiwara et al.	
	18	6121315		2000-09-19	Nair et al.	
	19	6143799		2000-11-07	Chowhan et al.	

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	20	6319464		2001-11-20	Asgharian	
	21	6348190		2002-02-19	Illes et al.	
	22	6482799		2002-11-19	Tuse et al.	
	23	6492361		2002-12-10	Muller et al.	
	24	6503497		2003-01-07	Chowhan et al.	
	25	6583124		2003-06-24	Asgharian	

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Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20020122831		2002-09-05	Mowrey-McKee et al.	
	2	20020123482		2002-09-05	Chowhan et al.	
	3	20050129771		2005-06-16	Asgharian	

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	1	2003-104870	JP		2003-04-09	Rohto Pharmaceutical Co., Ltd. / Kiyobashi		☒
	2	95/13050	WO		1995-05-18	Ciba-Geigy AG		☐
	3	2005/097067	WO		2005-10-20	Bausch & Lomb Incorporated		☐
	4	2008/042619	WO		2008-04-10	Alcon Manufacturing, Ltd.		☐

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Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	Kabara, et al., Preservative-Free and Self-Preserving Cosmetics and Drugs – Principles and Practice, Chapter 1, pages 1-14, Marcel Dekker, Inc., 1997	☐
	2	McCarthy, "Metal Ions and Microbial Inhibitors", Cosmetic & Toiletries, 100:69-72, 1985	☐
	3	McCarthy, et al., "The Effect of Zinc Ions on the Antimicrobial Activity of Selected Preservatives", Journal of Pharmacy and Pharmacology, Vol. 41 (1989)	☐
	4	PCT International Preliminary Report On Patentability for corresponding application PCT/US2007/079094 with mailing date December 11, 2008	☐

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	5	PCT International Search Report for corresponding application PCT/US2007/079094 with mailing date April 2, 2008	☐
	6	PCT Written Opinion for corresponding application PCT/US2007/079094 with mailing date April 2, 2008	☐
	7	Zeelie, et al., "Effects of Copper and Zinc Ions on the Germicidal Properties of Two Popular Pharmaceutical Antiseptic Agents, Cetylpyridinium Chloride and Povidone-iodine", Analyst, 123:503-507 (March 1998)	☐
	8	Zeelie, et al., "The Effects of Selected Metal Salts on the Microbial Activities of Agents used in the Pharmaceutical and Related Industries", Metal Compounds in Environment and Life, 4:193-200 (1992)	☐

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Examiner Signature	/Zohreh Fay/ (08/16/2012)	Date Considered	

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Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	5460834		1995-10-24	Bhagat	

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	1	20050214382		2005-09-29	Xia et al.	
	2	20070212420		2007-09-13	Xia et al.	
	3	20070297990		2007-12-27	Shah et al.	
	4	20100227003		2010-09-09	Shah et al.	

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	1	GUTTMAN, "Liquid gel therapy broadens role of dry eye product line", Ophthalmologytimes.com, 2006, pgs 33-34 and copyright notice	☐
	2	~~Illustration of packaging for Systane® free~~	☐

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Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12441995	CHOWHAN ET AL.
	Examiner	Art Unit
	ZOHREH A FAY	1612

SEARCHED

Class	Subclass	Date	Examiner
424	78.04	7/2/2012	ZF
514	738	7/2/2012	ZF
514	912	7/2/2012	ZF

SEARCH NOTES

Search Notes	Date	Examiner
West	6/19/2010	ZF
Inventor search	6/19/2010	ZF
updated	3/9/2011	ZF
updated	7/28/2011	ZF
Updated	2/21/2012	ZF
updated	7/2/2012	ZF

INTERFERENCE SEARCH

Class	Subclass	Date	Examiner
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	1	20110195132		2011-08-11	Kabra et al.	

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☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☒ See attached certification statement.

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Scott A. Chapple, Reg. #46,287/	Date (YYYY-MM-DD)	2011-12-13
Name/Print	Scott A. Chapple	Registration Number	46,287

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /ZF/

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /ZF/

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	12441995
Filing Date	2009-03-19
First Named Inventor	Masood A. Chowhan
Art Unit	1627
Examiner Name	Fay, Zohreh A.
Attorney Docket Number	2667 US F

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	5130298		1992-07-14	Cini et al.	
	2	5820822		1998-10-13	Kross	
	3	7074827		2006-07-11	Ueno	
	4	7445771		2008-11-04	Dassanayake et al.	

If you wish to add additional U.S. Patent citation information please click the Add button. Add

U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20060205725		2006-09-14	Ueno	
	2	20080075790		2008-03-27	Kabra et al.	

If you wish to add additional U.S. Published Application citation information please click the Add button. Add

FOREIGN PATENT DOCUMENTS Remove

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	12441995
Filing Date	2009-03-19
First Named Inventor	Masood A. Chowhan
Art Unit	1627
Examiner Name	Fay, Zohreh A.
Attorney Docket Number	2667 US F

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] ¡	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	98/10773	WO		1998-03-19	Richter Gedeon Vegyészeti		☐
	2	2007/106723	WO		2007-09-20	Bausch & Lomb Incorporated		☐
	3	2008/036847	WO		2008-03-27	Alcon Manufacturing, Ltd.		☐

If you wish to add additional Foreign Patent Document citation information please click the Add button Add

NON-PATENT LITERATURE DOCUMENTS Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	Bruce Grahn et al., "Zinc and the Eye", JOURNAL OF THE AMERICAN COLLEGE OF NUTRITION, 106-118, 4-2001	☐

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature	/Zohreh Fay/ (07/01/2012)	Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /ZF/

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

BIB DATA SHEET

CONFIRMATION NO. 7046

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
12/441,995	03/19/2009 RULE	424	1627	2667 US F

APPLICANTS

Masood A. Chowhan, Arlington, TX;
David J. Keith, Washington, MO;

**** CONTINUING DATA ****************************

This application is a 371 of PCT/US07/79094 09/20/2007
which claims benefit of 60/827,417 09/28/2006

**** FOREIGN APPLICATIONS **************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****

10/15/2009

Foreign Priority claimed ☐ Yes ☑ No 35 USC 119(a-d) conditions met ☐ Yes ☑ No Verified and Acknowledged /ZOHREH A FAY/ Examiner's Signature	☐ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		TX	0	8	2

ADDRESS

ALCON
IP LEGAL, TB4-8
6201 SOUTH FREEWAY
FORT WORTH, TX 76134
UNITED STATES

TITLE

SELF PRESERVED AQUEOUS PHARMACEUTICAL COMPOSITIONS

FILING FEE RECEIVED		
1440	FEES: Authority has been given in Paper No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

OK TO ENTER: /ZF/ (07/01/2012)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Masood A. Chowhan et al.

U.S. Serial No.: 12/441,995

Confirmation No.: 7046

Filed: March 19, 2009

Examiner: Fay, Zohreh A.

Group Art Unit: 1627

For: SELF PRESERVED AQUEOUS PHARMACEUTICAL COMPOSITIONS

CERTIFICATE OF FILING VIA EFS-WEB

I hereby certify that this correspondence is being submitted to the Mail Stop AF; Commissioner for Patents, P.O. Box 1450, Alexandria, VA. 22313-1450 via EFS-Web on this date:

June 15, 2012.

By: /Barbara McKenzie/
Barbara McKenzie

RESPONSE AFTER FINAL

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir or Madam:

This paper is submitted in response to the Final Office Action dated March 9, 2012, for which the Examiner has set a three-month period for response.

With this Response, Applicants have submitted a request for a one-month extension of time. If the U.S. Patent Office deems any fees to be deficient or absent, consider this paragraph a request and authorization to deduct said fees from Alcon Research, Ltd. Deposit Account No. 010682.

Reconsideration of the application is respectfully requested.

A listing of claims begins on page 2 of this paper.

Remarks begin on page 5 of this paper.

Issue Classification

Application/Control No.	Applicant(s)/Patent Under Reexamination
12441995	CHOWHAN ET AL.
Examiner	**Art Unit**
ZOHREH FAY	1627

ORIGINAL		INTERNATIONAL CLASSIFICATION														
CLASS	SUBCLASS	CLAIMED									NON-CLAIMED					
424	78.04	A	6	1	K	9 / 00 (2006.01.01)										

CROSS REFERENCE(S)					
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)				
514	738				
514	912				

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☒ T.D. ☐ R.1.47

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	11														
2	14														
3	15														
4	17														
5	20														
6	21														
7	23														
8	24														
9	25														
10	26														

NONE (Assistant Examiner) (Date)	**Total Claims Allowed:** 10	
/ZOHREH FAY/ Primary Examiner.Art Unit 1627 (Primary Examiner) (Date)	O.G. Print Claim(s) 1	O.G. Print Figure none

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Masood A. Chowhan et al.

U.S. Serial No.: 12/441,995

Confirmation No.: 7046

Filed: March 19, 2009

Examiner: Fay, Zohreh A.

Group Art Unit: 1627

CERTIFICATE OF FILING VIA EFS-WEB

I hereby certify that this correspondence is being submitted to the Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA. 22313-1450 via EFS-Web on this date:

October 23, 2012.

By: /Barbara McKenzie/
Barbara McKenzie

For: SELF PRESERVED AQUEOUS PHARMACEUTICAL COMPOSITIONS

AMENDMENT AFTER NOTICE OF ALLOWANCE FILED UNDER 37 C.F.R. 1.312

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir or Madam:

This paper is submitted in response to the Notice of Allowance dated August 28, 2012.

Applicants believe that no fees are due for the filing of this amendment. Should any request or fee be deficient or absent, consider this paragraph such a request and authorization to deduct said fees from Alcon Research, Ltd. Deposit Account No. 010682. Reconsideration of the application is respectfully requested.

A listing of claims begins on page 2 of this paper.

Remarks begin on page 5 of this paper.

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions and listings of claims in the application:

Claims 1-10 (canceled)

Claim 11 (currently amended): A multi-dose, self-preserved ophthalmic composition, said composition comprising:

a therapeutically effective amount of an ophthalmic therapeutic agent selected from the group consisting of beta-blockers, carbonic anhydrase inhibitors, prostaglandin analogs, neuroprotectants, anti-angiogenesis agents, quinolones, anti-inflammatory agents, growth factors, immunosuppressant agents and anti-allergic agents; and

a preservative system consisting essentially of:

i. borate at a concentration in the composition of 0.3 to 1.5 w/v% wherein the borate comprises one or more borates;

ii. polyol at a concentration in the composition of 0.6 to 2.0 w/v% wherein the polyol comprises sorbitol and propylene glycol; and

iii. zinc ions, wherein the zinc ions are provided by zinc chloride at a concentration in the composition of 0.0005 to 0.005 w/v %;

~~wherein the borate and polyol form a borate/polyol complex for enhancing the antimicrobial activity of the composition and~~ wherein the preservative system has sufficient antimicrobial activity to allow the composition to satisfy USP 26 preservative efficacy requirements.

Claim 12 (canceled)

Claim 13 (canceled)

Claim 14 (previously presented): A composition as in claim 11 wherein the therapeutic agent is a prostaglandin analog.

Claim 15 (previously presented): A composition as in claim 11 wherein the therapeutic agent is travoprost.

Claim 16 (canceled)

Claim 17 (currently amended) A method of enhancing the antimicrobial activity of an aqueous ophthalmic pharmaceutical composition ~~that~~, which comprises including a preservative system in the composition, the preservative system consisting essentially of:

i. borate at a concentration in the composition of 0.3 to 1.5 w/v% wherein the borate comprises one or more borates;

ii. polyol at a concentration in the composition of 0.6 to 2.0 w/v% wherein the polyol comprises sorbitol and propylene glycol; and

iii. zinc ions, wherein the zinc ions are provided by zinc chloride at a concentration in the composition of 0.0005 to 0.005 w/v %;

wherein:

~~i. the borate and polyol form a borate/polyol complex for enhancing the antimicrobial activity of the composition;~~

i.ii the preservative system has sufficient antimicrobial activity to allow the composition to satisfy USP 26 preservative efficacy requirements; and

ii.~~iii~~.the preservative the composition includes a therapeutically effective amount of an ophthalmic therapeutic agent selected from the group consisting of beta-blockers, carbonic anhydrase inhibitors, prostaglandin analogs, neuroprotectants, anti-angiogenesis agents, quinolones, anti-inflammatory agents, growth factors, immunosuppressant agents and anti-allergic agents.

Claim 18 (canceled)

Claim 19 (canceled)

Claim 20 (previously presented): A method as in claim 17 wherein the therapeutic agent is a prostaglandin analog.

Claim 21 (previously presented): A method as in claim 17 wherein the therapeutic agent is travoprost.

Claim 22 (canceled)

Claim 23 (previously presented): A composition as in claim 11 wherein the concentration of borate in the composition is 0.5-1.2 w/v%.

Claim 24 (previously presented): A composition as in claim 15 wherein the concentration of borate in the composition is 0.5-1.2 w/v%.

Claim 25 (previously presented): A method as in claim 17 wherein the concentration of borate in the composition is 0.5-1.2 w/v%.

Claim 26 (previously presented): A method as in claim 21 wherein the concentration of borate in the composition is 0.5-1.2 w/v%.

REMARKS

The Notice of Allowance allowed Claims 11, 14, 15, 17, 20, 21 and 24-25. Applicants thank Examiner Fay for the Notice of Allowance. Applicants submit herewith minor amendments to claims 11 and 17. The amendments are not considered to affect the patentability of the claims.

I. Claim Amendments

The amendments to claims 11 and 17 merely remove unneeded functional language from those claims. To the extent, if any, that these amendments should be considered to broaden the claims of the present application, Applicants provide the following explanations as required by 37 C.F.R. 1.111(c) and/or 37 C.F.R. 1.312.

(A) Why the amendment is needed

The amendment to the claims is needed to remove unnecessary functional language from the claims.

(B) Why the proposed amended or new claims require no additional search or examination

The amended claims require no additional search since the ingredients recited as part of the claimed compositions remain the same.

(C) Why the claims are patentable

The claims are patentable because the ingredients of the composition recited in the amended claims are identical to those recited prior to the present amendment.

(D) Why they were not presented earlier

Following receipt of the Notice of Allowance, a final review of the claims and prosecution history was conducted and it was concluded that the deleted functional language was unnecessary.

CONCLUSION:

Applicants respectfully request allowance of the pending claims of the present application in view of the above remarks. Should the Examiner have any questions regarding this Amendment, please feel free to contact the undersigned attorney at the phone number listed below.

Respectfully submitted,

ALCON RESEARCH, LTD.

October 23, 2012
Date

Scott A. Chapple
Reg. No. 46,287

Address for Correspondence:
Alcon Research, Ltd.
Scott A. Chapple, IP Legal
6201 S. Freeway, Mail Code TB4-8
Fort Worth, TX 76134-2099
Phone: 817-615-5288

Attorney Docket: 2667 US F

Electronic Acknowledgement Receipt

EFS ID:	14050010
Application Number:	12441995
International Application Number:	
Confirmation Number:	7046
Title of Invention:	SELF PRESERVED AQUEOUS PHARMACEUTICAL COMPOSITIONS
First Named Inventor/Applicant Name:	Masood A. Chowhan
Customer Number:	26356
Filer:	Scott Chapple/Barbara McKenzie
Filer Authorized By:	Scott Chapple
Attorney Docket Number:	2667 US F
Receipt Date:	23-OCT-2012
Filing Date:	19-MAR-2009
Time Stamp:	10:42:50
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		2667_US_F_Amend_102312.pdf	202892 d6af07a8cd77dcf143ed9e720805c8fc755f70b1	yes	6

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment after Notice of Allowance (Rule 312)	1	1
	Claims	2	4
	Applicant Arguments/Remarks Made in an Amendment	5	6
Warnings:			
Information:			
	Total Files Size (in bytes):	202892	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/441,995	03/19/2009	Masood A. Chowhan	2667 US F	7046

26356 7590 11/20/2012

ALCON
IP LEGAL, TB4-8
6201 SOUTH FREEWAY
FORT WORTH, TX 76134

EXAMINER	
FAY, ZOHREH A	

ART UNIT	PAPER NUMBER
1627	

NOTIFICATION DATE	DELIVERY MODE
11/20/2012	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):

patent.docketing@alconlabs.com

Response to Rule 312 Communication	Application No.	Applicant(s)
	12/441,995	CHOWHAN ET AL.
	Examiner	Art Unit
	ZOHREH FAY	1627

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

1. ☒ The amendment filed on *25 October 2012* under 37 CFR 1.312 has been considered, and has been:

   a) ☒ entered.

   b) ☐ entered as directed to matters of form not affecting the scope of the invention.

   c) ☐ disapproved because the amendment was filed after the payment of the issue fee.
   Any amendment filed after the date the issue fee is paid must be accompanied by a petition under 37 CFR 1.313(c)(1) and the required fee to withdraw the application from issue.

   d) ☐ disapproved. See explanation below.

   e) ☐ entered in part. See explanation below.

/Zohreh A Fay/
Primary Examiner, Art Unit 1627

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

26356 7590 08/28/2012

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6201 SOUTH FREEWAY
FORT WORTH, TX 76134

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

Barbara McKenzie (Depositor's name)
Barbara McKenzie (Signature)
November 27, 2012 (Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/441,995	03/19/2009	Masood A. Chowhan	2667 US F	7046

TITLE OF INVENTION: SELF PRESERVED AQUEOUS PHARMACEUTICAL COMPOSITIONS

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1740	$300	$0	$2040	11/28/2012

EXAMINER	ART UNIT	CLASS-SUBCLASS
FAY, ZOHREH A	1627	424-078040

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
- ☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 Scott A. Chapple
2
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: Alcon Research, Ltd.

(B) RESIDENCE: (CITY and STATE OR COUNTRY): Fort Worth, Texas

Please check the appropriate assignee category or categories (will not be printed on the patent): ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:
- ☒ Issue Fee
- ☒ Publication Fee (No small entity discount permitted)
- ☐ Advance Order - # of Copies .....

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
- ☐ A check is enclosed.
- ☐ Payment by credit card. Form PTO-2038 is attached.
- ☒ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number 010682 (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
- ☐ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.
- ☐ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature Scott A. Chapple Date 27 November 2012

Typed or printed name Scott A. Chapple Registration No. 46,287

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

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Electronic Patent Application Fee Transmittal

Application Number:	12441995
Filing Date:	19-Mar-2009
Title of Invention:	SELF PRESERVED AQUEOUS PHARMACEUTICAL COMPOSITIONS
First Named Inventor/Applicant Name:	Masood A. Chowhan
Filer:	Scott Chapple/Barbara McKenzie
Attorney Docket Number:	2667 US F

Filed as Large Entity

U.S. National Stage under 35 USC 371 Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Utility Appl issue fee	1501	1	1770	1770
Publ. Fee- early, voluntary, or normal	1504	1	300	300

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**2070**

Electronic Acknowledgement Receipt

EFS ID:	14317602
Application Number:	12441995
International Application Number:	
Confirmation Number:	7046
Title of Invention:	SELF PRESERVED AQUEOUS PHARMACEUTICAL COMPOSITIONS
First Named Inventor/Applicant Name:	Masood A. Chowhan
Customer Number:	26356
Filer:	Scott Chapple/Barbara McKenzie
Filer Authorized By:	Scott Chapple
Attorney Docket Number:	2667 US F
Receipt Date:	27-NOV-2012
Filing Date:	19-MAR-2009
Time Stamp:	15:42:31
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$2070
RAM confirmation Number	2493
Deposit Account	010682
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. 1.492 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Issue Fee Payment (PTO-85B)	2667_US_F_Fee-Transmittal_112712.pdf	150236 fdbbb86dddd00a9b5cf28270f65c698f3b0ffcad	no	1
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	32173 f1880bb32f2ebbbba579c64ec408c499c66d6d26c	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	182409		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/441,995	03/19/2009	Masood A. Chowhan	2667 US F	7046

26356 7590 02/11/2013

ALCON
IP LEGAL, TB4-8
6201 SOUTH FREEWAY
FORT WORTH, TX 76134

EXAMINER	
FAY, ZOHREH A	

ART UNIT	PAPER NUMBER
1629	

NOTIFICATION DATE	DELIVERY MODE
02/11/2013	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):

patent.docketing@alconlabs.com

Response to Rule 312 Communication	Application No. 12/441,995	Applicant(s)
	Examiner	Art Unit

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

1. ☒ The amendment filed on *23 October 2012* under 37 CFR 1.312 has been considered, and has been:

a) ☒ entered.

b) ☐ entered as directed to matters of form not affecting the scope of the invention.

c) ☐ disapproved because the amendment was filed after the payment of the issue fee.
Any amendment filed after the date the issue fee is paid must be accompanied by a petition under 37 CFR 1.313(c)(1) and the required fee to withdraw the application from issue.

d) ☐ disapproved. See explanation below.

e) ☐ entered in part. See explanation below.

/ A. Marty Willis /

A. Marty Willis

Publishing Division

Office of Data Management

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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/441,995	03/05/2013	8388941	2667 US F	7046

26356 7590 02/13/2013

ALCON
IP LEGAL, TB4-8
6201 SOUTH FREEWAY
FORT WORTH, TX 76134

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

Masood A. Chowhan, Arlington, TX;
David J. Keith, Washington, MO;