

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-193

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 22-193

SUPPL #

HFD # 520

Trade Name Navstel Intraocular Irrigating Solution

Generic Name balanced salt ophthalmic solution with hypromellose, dextrose and glutathione

Applicant Name Alcon Inc.

Approval Date, If Known July 24, 2008

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b) (1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 18-469

BSS PLUS Sterile Intraocular Irrigating Solution (balanced salt solution enriched with bicarbonate, dextrose, and glutathione)

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a)

is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

(C 02 39, C 03 33, C 04 14, and C 04 18)

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

Investigation #1

!

YES

!

! NO

Explain:

! Explain:

Investigation #2

!

YES

!

! NO

Explain:

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

Name of person completing form: William M. Boyd, M.D.

Title: Lead Medical Officer

Date: 7/24/08

Name of Office/Division Director signing form: Wiley Chambers, M.D.

Title: Acting Division Director, DAIOP

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

William Boyd
7/24/2008 02:57:01 PM

Wiley Chambers
7/24/2008 03:32:56 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 22-193

Supplement Number: _____

NDA Supplement Type (e.g. SE5): S-3

Division Name: Division of Anti-Infective and Ophthalmology Products

PDUFA Goal Date: 7/24/08

Stamp Date: 9/24/07

Proprietary Name: Navstel

Established/Generic Name: (salts, hypromellose, and dextrose ophthalmic solution)

Dosage Form: solution

Applicant/Sponsor: Alcon

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) _____
- (2) _____
- (3) _____
- (4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1

(Attach a completed Pediatric Page for each indication in current application.)

Indication: ___ for use as an intraocular irrigating solution during surgical procedures involving perfusion of the

eye

Q1: Is this application in response to a PREA PMC/PMR? Yes Continue

No Please proceed to Question 2.

If Yes, NDA/BLA#: _____

Supplement #: _____

PMC/PMR #: _____

Does the division agree that this is a complete response to the PMC/PMR?

Yes. Please proceed to Section D.

No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW active ingredient(s) (includes new combination); indication(s); dosage form; dosing regimen; or route of administration?*

(b) No. PREA does not apply. **Skip to signature block.**

* **Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

Q3: Does this indication have orphan designation?

Yes. PREA does not apply. **Skip to signature block.**

No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply.
- Partial Waiver for selected pediatric subpopulations (Complete Sections B)
- Deferred for some or all pediatric subpopulations (Complete Sections C)
- Completed for some or all pediatric subpopulations (Complete Sections D)
- Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
- Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- Necessary studies would be impossible or highly impracticable because:
- Disease/condition does not exist in children
- Too few children with disease/condition to study
- Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

			Reason (see below for further detail):				
	minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

Necessary studies would be impossible or highly impracticable because:

Disease/condition does not exist in children

Too few children with disease/condition to study

Other (e.g., patients geographically dispersed): _____

Not meaningful therapeutic benefit:

Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)

Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)

Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)

Δ Formulation failed:

Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the

pediatric subpopulations.

Action C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
<input checked="" type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input checked="" type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population	minimum	maximum	Extrapolated from:	
			Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications.

Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Lori Gorski
Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Lori Gorski
7/25/2008 04:19:22 PM

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: July 2, 2008

TO: Lori Gorski, Regulatory Project Manager
William Boyd, M.D.
Medical Officer
Division of Anti-Infective and Ophthalmology Drug Products

FROM: Susan D. Thompson, M.D.
Medical Officer
Good Clinical Practice Branch 2
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Acting Branch Chief
Good Clinical Practice Branch 2
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 22-193

APPLICANT: Alcon, Inc.

DRUG: NGOIS: Next Generation Ophthalmic Irrigating Solution (balanced salt
intraocular irrigating solution containing a bicarbonate buffer. _____
glutathione, and hydroxypropyl methylcellulose) **b(4)**

NME: No

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATIONS: 1. Use as an intraocular irrigating solution during surgical procedures
involving perfusion of the eye

CONSULTATION REQUEST DATE: June 1, 2008

DIVISION ACTION GOAL DATE: July 1, 2008

PDUFA DATE: July 24, 2008

I. BACKGROUND: Next Generation Ophthalmic Irrigating Solution (NGOIS) was developed by Alcon to be a novel irrigating solution with improved physical properties to be used during intraocular surgery, including cataract extraction/IOL implantation and epimacular membrane removal/vitreotomy. The majority of cataracts are currently removed by phacoemulsification, which uses a surgical hand-piece with a tip vibrating at ultrasonic frequencies. The energy generated by this tip causes the disintegration of the cataractous lens and typically creates smaller, more highly mobile lens fragments in the process. These lens fragments may damage surrounding tissue and travel to the anterior chamber. Current practice is to inject a viscoelastic material into the anterior chamber prior to phacoemulsification in order to prevent the lens particles from damaging the corneal endothelium. The majority of the viscoelastic may be aspirated from the eye or exudes from the wound during the surgical procedure resulting in the loss or a reduction of endothelial cell protection during phacoemulsification. Damage to ocular tissues may also result from the turbulent flow of intraocular fluids or from bubbles generated by the phacoemulsification hand-piece. The turbulent flow of liquids may cause lens fragments to collide with corneal endothelium cells and other intraocular tissues, resulting in iatrogenic trauma.

Epimacular membranes are collections of collagenous cells that occur on the inner surface of the central retina. These membranes have contractile properties resulting in retinal distortion with resultant visual changes. Epimacular membranes can be associated with a variety of ocular conditions, including posterior vitreous detachment, retinal tears, retinal detachments, retinal vascular occlusive disease, ocular inflammatory diseases, and vitreous hemorrhage; they may also be idiopathic. The treatment of epimacular membranes is removal of the epimacular membrane and vitrectomy. Turbulence in the posterior segment during this procedure leading to iatrogenic retinal movement may complicate posterior segment surgery by restricting the surgeon from working close to the retina which could increase the risk of incarceration. Reduction in turbulent flow would provide increased intraoperative control and a higher safety margin during posterior segment procedures.

NGOIS is a sterile, physiological, intraocular irrigating solution, for use during anterior segment surgical procedures. It contains no pharmacologically active ingredients. The composition of NGOIS is chemically similar to that of human aqueous humor with an additional component, hydroxypropyl methylcellulose, which is added _____

_____ NGOIS also contains essential ions, a bicarbonate glucose (_____) and glutathione _____

b(4)

NGOIS will be used for intraocular irrigation during surgical procedures involving the eye.

The Sponsor proposes that the improved physical properties of NGOIS (e.g., flow characteristics/fluid dynamics) relative to currently marketed ophthalmic irrigating solutions will:

_____ b(4)

The sponsor's proposed indication for NGOIS is use as an intraocular irrigating solution during surgical procedures involving perfusion of the eye. The adverse event profile would be expected to be benign, in that there are no pharmacologically active ingredients and the product is used only briefly during surgery.

The development program for NGOIS includes two Phase 2 studies, 1 small Phase 3 study in a pediatric population, and two pivotal Phase 3 controlled studies. The two Phase 3 studies were selected for audit and are briefly summarized below.

Protocol C-04-14: Clinical Evaluation of the Safety and Efficacy of Next Generation Ophthalmic Irrigating Solution Compared to BSS PLUS for Use During Cataract Extraction and IOL Implantation

Study C-04-14 is a multi-center, observer- and patient-masked, active-controlled, randomized parallel group study conducted between September 27, 2004 and July 19, 2005. The study enrolled patients of any age and either sex requiring cataract extraction with the implantation of a posterior chamber intraocular lens. The following conditions were excluded: glaucoma, ocular hypertension in the operative eye at baseline, any abnormality precluding reliable tonometry, any condition resulting in a poor quality endothelial cell image in the operative eye, any patient at increased risk of corneal decompensation, planned multiple procedures during cataract/IOL implantation surgery, lens pseudoexfoliation syndrome where glaucoma or zonular compromise was present in the operative eye, previous ocular trauma to the operative eye, a history of chronic or recurrent inflammatory eye disease, diabetic retinopathy, previous retinal detachment, clinically significant RPE/macular changes, uncontrolled diabetes mellitus, congenital ocular anomaly (excluding congenital cataract), iris atrophy in the operative eye, a visually nonfunctional fellow eye, use of an investigational intraocular lens, or previous eye enrolled in the study. Patients were randomly assigned in a 1:1 ratio to receive 1 of 2 solutions for intraocular irrigation during cataract/IOL surgery: NGOIS or BSS PLUS in volumes sufficient to irrigate adequately during surgery. Patients were examined through day 90 to evaluate safety and efficacy.

Subjects were evaluated at screening/baseline (-6 weeks to -1 day), on day 0 (day of cataract/IOL surgery), at 6-(\pm 2 hours) and 24-hour (\pm 4 hours) postoperative visits, at days 3 (\pm 1 day), 7 (\pm 2 days), 30 (\pm 7 days), and 90 (\pm 14 days) (or at the day of patient discontinuation from the study).

Clinical evaluations at screening/baseline included best corrected logMAR visual acuity in both eyes, a slit-lamp examination, central corneal thickness (3 measurements), central endothelial cell photography (2 photographs), IOP measurement, dilated fundus examination

(both eyes) and an estimate of lens hardness. The surgical visit data included a questionnaire completed by the surgeon describing the average turbulence during cataract extraction, followability to the phacoemulsification tip, the viscoelastic retention and reinstallation in the anterior chamber, and an evaluation of the actual lens hardness. At the 6-hour and 3-day examinations, the following were performed and/or recorded: IOP measurement, any new IOP-reducing therapy, central corneal thickness (3 measurements), any change in surgery related medications and concurrent ocular and systemic medications and systemic disease/conditions since surgery, surgically related optical symptoms, and adverse events. The same evaluations were performed at the 24-hour, day 7, and day 30 examinations; in addition, the best corrected logMAR visual acuity and central corneal thickness (3 measurements) were determined and a slit-lamp examination performed. At 90 days, these procedures will be performed, and in addition, central endothelial cell photography (2 photographs) will be performed.

The primary efficacy endpoint is the percent change in endothelial cell density at day 90 in the per protocol data set. The secondary efficacy endpoints are the best correct logMAR visual acuity, central corneal thickness, flow characteristics of the irrigating solution (turbulence and followability to the phacoemulsification tip) and retention of the viscoelastic derived from the surgeon questionnaire.

Brief Summary of Results

In this clinical study, 13 investigators enrolled 369 patients who were evaluable for safety and intent-to-treat analyses (184 NGOIS and 185 BSS PLUS). Of the 369 patients enrolled, 344 were evaluable for efficacy in the per protocol analyses (173 NGOIS and 171 BSS PLUS). Of the 344 randomized, 7 patients discontinued from the study: 4 due to adverse events (all in the NGOIS arm) and 3 due to lost to follow-up (all in the BSS PLUS arm).

Protocol violations resulted in the exclusion of 25 patients from the per protocol analysis (five due to not meeting inclusion/exclusion criteria, 15 due to surgical complications, 4 due to disallowed surgical procedures, and 1 due to receiving incorrect test article); exclusions occurred in 11 patients in the NGOIS arm and 14 patients in the BSS arm.

Treatment groups were well matched with respect to demographic (sex and race) and baseline characteristics (mean central corneal thickness, mean central endothelial cell density, and best corrected visual acuity). In the ITT analysis, 46.6% of the patients were male, and the majority 74.5% were Caucasian; the most common iris color was brown (47.7%). Similar results were observed for patients in the per protocol data set. In the per protocol dataset, those patients receiving NGOIS demonstrated a 7.7% mean endothelial cell density loss at the post-operative Day 90 visit relative to baseline compared to a mean loss of 9.6% in the BSS PLUS treatment group. The two-sided 95% confidence interval on the treatment-group difference of 1.9% was (-1.5%, 5.2%) The FDA-established criterion for non-inferiority was based on an observed absolute endothelial cell loss within the NGOIS treatment group less than or equal to 10% from baseline. In addition, the left side of a two-sided 95% confidence limit on the treatment difference in percent change in endothelial cell density must be greater than -7.5%. Therefore, the Sponsor concludes that the results of the study support noninferiority of BGOIS when compared to BSS at post-operative day 90 in mean endothelial cell density loss.

No serious, treatment-related adverse events were reported in either treatment group. Adverse events in the overall safety population were mostly nonserious, usually mild or moderate in intensity, generally resolved with or without treatment, and did not interrupt patient continuation (the exception being a patient who died due to congestive heart failure, unrelated to therapy). The most common adverse event in both arms was increased intraocular pressure. No safety concerns were identified based upon an analysis of changes from baseline for intraocular pressure, ocular signs, and dilated fundus parameters.

The Sponsor concludes that NGOIS is safe and well-tolerated in patients undergoing cataract surgery and intraocular lens implantation.

Protocol C-04-18: Clinical Evaluation of the Safety of Next Generation Ophthalmic Irrigating Solution Compared to BSS Plus® for Use During Surgery for Removal of Epimacular Membrane and Vitrectomy

Study C-04-18 is a multi-center, observer- and patient-masked, active-controlled, randomized parallel group clinical trial conducted between October 19, 2005 and March 21, 2007. The study enrolled adults of age 18 years or older of any lens status with an epimacular membrane who would benefit from vitrectomy and membrane removal. Patients were permitted to have had a previous retinal detachment surgery in the operative eye if the retina had been completely attached for a minimum of 90 days prior to the preoperative screening/baseline visit. The following conditions were excluded: glaucoma with a cup-to-disc ratio >0.8 in the operative eye, glaucoma patients with a baseline IOP > 21 mm Hg in the operative eye while on IOP lowering medication, previous glaucoma filtration surgery in the operative eye, history of an attack of acute narrow angle-closure glaucoma or chronic angle-closure glaucoma in the operative eye, ocular hypertension in the operative eye at baseline, any abnormality precluding reliable tonometry in either eye, other planned surgical procedures, previous ocular trauma to the operative eye, a history of chronic or recurrent inflammatory eye disease, diabetic retinopathy, retinal detachment in the operative eye within 90 days of the preoperative screening/baseline visit, silicone oil currently present in the operative eye, significant proliferative vitreoretinopathy other than epimacular membrane in the operative eye, history of or current branch or central retinal vein or artery occlusion in the operative eye, history of chronic, recurrent, or current inflammatory eye disease in the operative eye, myopes with a spherical equivalent greater than or equal to 8 diopters, patients with proliferative diabetic retinopathy in the operative eye (except mild, non-proliferative diabetic retinopathy in the operative eye, defined as microaneurysms only), RPE/macular changes in the operative eye associated with a best-corrected Snellen visual acuity worse than 20/40, a visually nonfunctional fellow eye, or previous eye enrolled in the study. Patients were randomly assigned to treatment groups sequentially within each investigational site to receive 1 of 2 solutions for intraocular irrigation during vitrectomy and epimacular membrane removal: NGOIS or BSS Plus® in volumes sufficient to irrigate adequately during surgery. Patients were examined through day 90 to evaluate safety.

Subjects were evaluated at screening/baseline (-6 weeks to -1 day), on day 0 (day of cataract/IOL surgery), at a 24-hour (± 4 hours) postoperative visit, at days 7 (± 2 days), 14 (± 2

days), 30 (\pm 5 days), day 60 (\pm 7 days), and 90 (- 7 to \pm 14 days) (or at the day of patient discontinuation from the study).

Clinical evaluations at screening/baseline included best corrected logMAR visual acuity in both eyes, full-field electroretinogram (ERG) in both eyes (selected sites only), a slit-lamp examination of intraocular inflammation and of the lens, Goldmann IOP measurement in both eyes, and dilated fundus examination of both eyes. The surgical visit data included recording of changes in concurrent ocular and systemic medications, irrigating solution data, surgical information, surgery related medications, and adverse events. At the 4-hour postoperative examination, the following evaluations were performed: Goldmann IOP measurement, any new IOP-reducing therapy, slit-lamp examination of intraocular inflammation, dilated fundus examination, any change in surgery related medications and concurrent medications, systemic conditions and non-surgically related ocular conditions since surgery, surgically related optical conditions, and adverse events. The same evaluations were performed at the day 7 and day 14 examinations; in addition, the best corrected logMAR visual acuity was determined. At days 30 and 60, these procedures were performed, and in addition, slit-lamp assessment of the lens was performed. At day 90, these procedures were performed, and in addition, full-field ERG of both eyes was performed at selected study sites and an Exit form completed.

The primary efficacy endpoint was the percentage of patients with maintenance or improvement in best-corrected visual acuity at the postoperative day 90 visit relative to baseline in the per protocol data set. Safety assessments included an ERG; slit-lamp assessment of intraocular inflammation (aqueous cells and flare), corneal edema, and the lens; dilated fundus examination of the retina/macula/choroid, optic nerve, and vitreous haze; IOP measurements; and adverse events.

Brief Summary of Results

In this clinical study, 31 investigators enrolled 344 patients who were evaluable for safety and intent-to-treat analyses (168 NGOIS and 176 BSS Plus[®]). Of the 344 patients enrolled, 333 were evaluable for efficacy in the per protocol analyses (164 NGOIS and 169 BSS Plus[®]). One patient treated with NGOIS died of colon cancer not related to the test article; three other patients in the NGOIS discontinued the study due to adverse events not related to the test article (glaucoma, pleural effusion, and chronic renal failure). Three patients in the BSS arm discontinued therapy due to loss to follow-up. Protocol violations resulted in the exclusion of 11 patients from the per protocol analysis: 10 due to undergoing a second ocular surgery prior to Day 90 (4 in the NGOIS arm and 6 in the BSS arm), and 1 due to receiving silicone oil during the study surgery (BSS arm).

Treatment groups were well matched with respect to demographic (sex and race) and baseline (best-corrected logMAR visual acuity at baseline) characteristics. In the ITT analysis, 45.9% of the patients were male, and the majority 91.9% were Caucasian; the most common iris colors were brown (38.1%) and blue (35.5%). Similar results were observed for patients in the per protocol data set. The mean age at the time of enrollment was 70.7 years and ranged from 37 to 92 years in the intent-to-treat data set. In the per protocol dataset, 80.6% of the patients receiving NGOIS demonstrated maintenance or improvement in best-corrected logMAR visual acuity at at the post-operative Day 90 visit relative to baseline compared to 87.3% in the BSS

Plus treatment group. The two-sided 95% confidence interval on the treatment-group difference of -6.7% was (-14.7%, 1.2%) The FDA-established noninferiority criterion was 15%. The Sponsor concludes that the lower confidence limit was within the prespecified noninferiority criterion of -15%, indicating that NGOIS is noninferior to BSS Plus[®] for maintenance or improvement in best-corrected logMAR visual acuity at the postoperative Day 90 visit. The intent-to-treat results were similar.

Adverse events in the overall safety population were mostly nonserious and did not interrupt patient continuation in the study with 4 exceptions, as described above. Four patients in the NGOIS arm discontinued from the study due to adverse events not related to study drug (death due to colon cancer, glaucoma, pleural effusion, and chronic renal failure). No serious treatment-related adverse events were reported in either treatment group. Treatment-related nonserious adverse events were experienced by 1 patient in the NGOIS treatment group (uveitis, iris adhesions, iritis, and increased IOP) and 1 patient in the BSS Plus[®] treatment group (increased IOP). One patient in each treatment group experienced clinically relevant treatment-related changes from baseline in intraocular pressure that resolved with treatment; this did not affect patient continuation in the study. No clinically relevant treatment-related changes from baseline in best-corrected logMAR visual acuity, inflammatory cells, aqueous flare, corneal edema, vitreous haze, optic nerve, retina/macula/choroid, lens, or ERG were observed. The Sponsor concludes that no untoward safety issues were identified in a population of adult and elderly patients exposed to NGOIS while undergoing surgery for epimacular membrane removal and vitrectomy.

There were no specific concerns identified regarding the conduct of these two clinical trials. The two sites were chosen based on high enrollment numbers.

II. RESULTS (by Site):

Name of CI, IRB, or Sponsor Location	Protocol #: and # of Subjects:	Inspection Date	Interim Classification	Final Classification
Arthur Fishman, M.D.	Protocol C-04-14: 44 enrolled, 15 audited	5/5-5/9/08 and 5/12/08	OAI	VAI
Sunil Gupta, M.D.	Protocol C-04-18: 26 enrolled, 13 audited	4/28-4/30/08	NAI	NAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.

1. Arthur M. Fishman, M.D.
Eye Surgery Associates
603. N. Flamingo Road
Suite 250
Pembroke Pines, FL 33028

- a. What was inspected:** Inspection was conducted in accordance with Compliance Program 7348.811. In Study C-04-14, 48 subjects were screened, 44 subjects were enrolled, and 15 subjects were audited. There were no limitations to the inspection. Dr. Fishman's IRB and sponsor correspondence files were reviewed. Records of 15 study subjects who received the drug were reviewed for protocol adherence, documentation practices, adverse events, drug accountability, adherence to inclusion/exclusion criteria, review of medications allowed during the study, and informed consent procedures. All 44 consent forms for subjects enrolled in the study were checked.
- b. General observations/commentary:** Several deviations from FDA regulations were noted, and a Form FDA 483 was issued for these violations. The inspection documented that Dr. Fishman did not obtain informed consent prior to experimental drug administration and did not prepare and maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation, in violation of 21 CFR 312.62(b)

Failure to obtain informed consent in accordance with 21 CFR 50 from each human subject prior to drug administration **b(6)**

Specifically, Subject 2512 did not sign a study informed consent form. Dr. Fishman stated during the inspection that this subject had pain in her hand during their office visit, and a person described as "family friend" signed the informed consent on 12/20/04. The exhibits include another consent form signed by the subject herself on 8/20/04.

Failure to prepare and maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation pursuant to 21 CFR 312.62(b)

1. Four subjects () were screened but not enrolled in the study. There is no record in these subject's medical charts documenting that the screening took place, what activities were performed, and why the subjects failed screening. **b(6)**
2. The data for determination of the primary efficacy endpoint were not stored in a secure location. The primary efficacy endpoint for this protocol was the percent change from baseline in endothelial cell density at day 90 in the per protocol data set determined on an endothelial cell photograph. After a photograph was taken, Dr. Fishman's assistant would download the photo to a 3.5 inch floppy disc and mail the floppy disc to the sponsor. The photographs downloaded to the floppy disc were not write protected and

could potentially be manipulated. The inspector found that Dr. Fishman did not conduct a software validation for obtaining and storing the endothelial cell photographs which were stored as electronic records. The endothelial cell photographs were stored electronically on a computer hard drive in one of the shared examination rooms at Dr. Fishman's ophthalmology practice. According to the inspector, the computer was not password protected, and all clinic personnel (in addition to study personnel) had access to the photographs. The photographs were not stored in pdf format. In addition, when the inspector attempted to view the photographs on day 5 of the inspection, the Research Coordinator and an office computer specialist were unable to retrieve any study subject endothelial cell photographs. On the next day of the inspection, the Research Coordinator stated that she had contacted the sponsor and could now link the database containing the endothelial cell photographs with the appropriate software, which that the photographs could be viewed. The Research Coordinator who participated in the study was no longer in Dr. Fishman's practice. There is no evidence from the EIR that the endothelial cell photographs were altered or that data integrity was impacted.

An investigation was not conducted in accordance with the signed statement of the investigator and the investigational plan in violation of 21 CFR 312.60.

1. Two subjects did not meet inclusion criteria and were included in the study. b(6)
 - i. At baseline on 10/28/04, Subject 2502 — had guttata documented in the ocular medical history (a protocol exclusion) and the endothelial photograph did not have clearly distinguishable cell borders, as required by the protocol.
 - ii. Subject 2523 — had an intraocular pressure (IOP) of 21 at the screening visit on 2/17/05; according to the protocol, subjects with an IOP of greater than or equal to 21 mm Hg were to be excluded. b(6)
2. Four subjects did not sign informed consent forms and had study related activities performed such as LogMARs, pachymetry testing, and endothelial cell photos. These are the same four subjects (————
—————) who failed screening without documentation described above. These study procedures were noninvasive and did not involve a safety risk to the screened subjects. b(6)
3. There was no evidence that Dr. Fishman evaluated the baseline visit endothelial cell photographs for potential corneal decompensation, an exclusion criterion according to the protocol, for Subjects 1504 —, 2502 —, and 2523 —. The protocol states that the investigator should evaluate the baseline endothelial cell photographs, both for the b(6)

ability to distinguish endothelial cell borders and to minimize the risk of corneal decompensation. Dr. Fishman stated to the inspector that he did not personally evaluate the baseline cell photographs. Corneal decompensation (corneal edema and opacification) is a nonspecific corneal response to mechanical or chemical injury which occurs in <0.05% of cataract surgeries in the U.S. each year (———, April 24, 1998, 47(15):306-308.) An increased risk of corneal decompensation can be predicted based on pre-operative morphology of endothelial cells. The study report for protocol C-04-14 states that no serious treatment related adverse events occurred. There were no clinically relevant treatment related changes from baseline in corneal edema, aqueous flare, or retina/macula/choroid in this study. Therefore, although Dr. Fishman did not follow the investigational plan, his failure to personally evaluate the baseline endothelial cell photos did not impact patient safety. Dr. Fishman's failure to look at the baseline endothelial cell photographs was discussed with Dr. Lucious Lim (covering for Dr. Boyd), who felt that this omission would not affect data integrity, and agreed that given the outcome of the study, that patient safety was not compromised.

b(6)

4. There was no written documentation delegating authority to three personnel who conducted study activities. ——— (Study Coordinator), ——— (Assistant Coordinator), and ——— (Registered Nurse) performed LogMARs, endothelial cell photography, pachymetry testing, masking of the study drug, study drug storage, filling out case report forms, filled out source documents, obtained informed consent, documented institutional review board and sponsor communications.

b(4)

- c. **Assessment of data integrity:** There were informed consent, recordkeeping, and protocol violations which occurred at this site. The informed consent, failure to document screening results, and protocol violations are unlikely to impact the final outcome of the study, nor does it appear that the rights, safety, and welfare of any of the randomized subjects was compromised. The storage conditions for the electronic data relevant to the determination of the primary efficacy endpoint are of more concern. Determination of the change in determination of the endothelial cell density was made by the sponsor using the photographs transmitted by the site; data on these floppy discs was not write protected. The photographs at the site were stored on a computer hard drive where any clinic personnel could access them, and in such a form that alteration would be possible. Dr. Fishman stated during the inspection that he had not received training by the sponsor in software and electronic data storage. Although it is theoretically possible that the photographs could have been altered at Dr. Fishman's site, there is no evidence that they were in fact altered. The data appear acceptable to use in support of the NDA.

2. **Sunil Gupta, M.D.**
5150 N. Davis Hwy
Retina Specialists
Pensacola, FL 32503

- a. **What was inspected:** Inspection was conducted in accordance with Compliance Program 7348.811. In Study C-04-18, 26 subjects were enrolled, and 13 subjects were audited. There were no limitations to the inspection. Dr. Gupta's IRB and sponsor correspondence files were reviewed. Records of 13 study subjects who received the drug were reviewed for protocol adherence, documentation practices, adverse events, concurrent medications, drug accountability, adherence to inclusion/exclusion criteria, and informed consent procedures. All 26 consent forms for subjects enrolled in the study were checked.
- b. **General observations/commentary:** The inspection conducted on 4/28-4/30/08 found that the Principal Investigator and Sub-investigators followed the protocol and enrolled subjects that met the established criteria, obtained the required informed consent prior to or at the time of enrollment and corresponded with the IRB regarding approvals, annual reviews and changes as required. There were no adverse events to report during the course of the clinical study at Dr. Gupta's site. No Form FDA 483, Inspectional Observations was issued.
- c. **Assessment of data integrity:** The data from Dr. Gupta's site appear acceptable for use in support of the NDA.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

In general, the audited sites adhered to the applicable regulations and good clinical practices governing the conduct of clinical investigations. The inspection of documents supports that audited subjects exist, met eligibility criteria, received assigned study medication, adhered to protocol, and signed informed consent documents. The inspections documented minor regulatory violations at the site of Dr. Fishman regarding protocol adherence, recordkeeping, and informed consent violations. Although failure to keep electronic records in a protected state at the site raised the question of whether alterations may have been made in the endothelial cell photographs used to determine the primary efficacy endpoint, there is no evidence that such alterations occurred and no evidence that data integrity was impacted. Dr. Fishman's failure to look at the baseline endothelial cell photographs was discussed with Dr. Lucious Lim of the Division of Anti-Infective and Ophthalmology Drug Products (covering for Dr. Boyd), who felt that this omission would not affect data integrity, and agreed that given the outcome of the study, that patient safety was not compromised. There were no significant violations at Dr. Gupta's site. In general, the studies appear to have been conducted adequately, and the data generated by these sites may be used in support of the indication.

{See appended electronic signature page}

Susan D. Thompson, M.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Acting Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

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/s/

Susan Thompson
7/3/2008 11:41:20 AM
MEDICAL OFFICER

Tejashri Purohit-Sheth
7/3/2008 11:43:26 AM
MEDICAL OFFICER



FILING COMMUNICATION

NDA 22-193

Alcon Inc.
c/o Alcon Research Ltd.
Attention: Sarah J. Cantrell
Assistant Director, Regulatory Affairs
6201 South Freeway
Fort Worth, TX 76134-2099

Dear Ms. Cantrell:

Please refer to your new drug application (NDA) dated September 21, 2007, received September 24, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for balanced salt intraocular irrigating solution enriched with bicarbonate, dextrose, glutathione and hypromellose.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application was considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is Standard. Therefore, the user fee goal date is July 24, 2008.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have submitted pediatric studies with this application for pediatric patients aged 90 days to 18 years. Once the review of this application is complete we will notify you whether you have fulfilled the pediatric study requirement for this application.

If you have any questions, call Lori Gorski, Regulatory Project Manager, at (301) 796-0722.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, M.D.
Acting Director
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

Wiley Chambers
12/5/2007 01:45:35 PM



NDA 22-193

NDA ACKNOWLEDGMENT

Alcon Inc.
c/o Alcon Research Ltd.
Attention: Sarah J. Cantrell
6201 South Freeway
Fort Worth, TX 76134-2099

Dear Ms. Cantrell:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: balanced salt intraocular irrigating solution enriched with bicarbonate, dextrose, glutathione and hypromellose

Date of Application: September 21, 2007

Date of Receipt: September 24, 2007

Our Reference Number: NDA 22-193

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 22, 2007, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must be in the Prescribing Information (physician labeling rule) format.

The NDA number provided above shown above be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Infective and Ophthalmology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/cder/ddms/binders.htm>.

If you have any questions, call Lori Gorski Regulatory Project Manager, at (301) 796-0722.

Sincerely yours,

{See appended electronic signature page}

Maureen P. Dillon-Parker
Chief, Project Management Staff
Division of Anti-Infective and Ophthalmology
Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

Maureen Dillon-Parker
10/11/2007 01:28:16 PM
NDA 22-193; Ack Ltr



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 64,320

Alcon Inc.
c/o Alcon Research Ltd.
Attention: Sarah J. Cantrell
Sr. Manager, Regulatory Affairs
6201 South Freeway
Fort Worth, Texas 76134-2099

Dear Ms. Cantrell:

Please refer to your Investigational New Drug Application (IND) for ~~_____~~ Intraocular Irrigating Solution. **b(4)**

We also refer to the meeting between representatives of your firm and the FDA on May 18, 2005. The purpose of the meeting was to discuss the planned clinical studies C-04-18 and C-04-64 and to clarify outstanding issues regarding the special protocol assessment request.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Lori M. Gorski, Project Manager, at (301) 827-2090.

Sincerely,

{See appended electronic signature page}

Janice M. Soreth, M.D.
Director
Division of Anti-Infective and Ophthalmology
Products, HFD-520
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure



MEETING MINUTES

Division of Anti-Infective and Ophthalmology Products, HFD-520

Meeting Date: May 18, 2005

Time: 3:00 PM EST

Application: IND 64,320

Meeting Type: Clarification on SPA response

Drug: Intraocular Irrigating Solution

Sponsor: Alcon

FDA PARTICIPANTS:

Lori Gorski, Project Manager
Wiley Chambers, Deputy Director
Jennifer Harris, Medical Officer
Lucious Lim, Medical Officer
Alison Rodgers, Project Manager
Rhea Lloyd, Medical Officer
Martin Nevitt, Medical Officer

LIST OF SPONSOR PARTICIPANTS:

Michael E. Pflieger, Senior Director, Regulatory Affairs
Angela C. Kothe, Associate Director, Regulatory Affairs
Kerry Markwardt, Director, Surgical Therapeutics
Dana P. Sager, Assistant Director, Clinical Sciences
F. Darell Turner, Senior Director, Biostatistics and Data Mgmt
Susan Potts, Manager, Biostatistics

QUESTIONS

1. Clinical Protocol C-04-18 (Posterior Segment Study)

In response to the Agency's request to add a clinically relevant primary endpoint to future efficacy phases of the clinical trial, Alcon has added maintenance or improvement in best corrected logMAR visual acuity at the Day 90 visit as the primary endpoint. Does the Agency agree that this is an acceptable clinically relevant endpoint?

Response: *Yes, maintenance or improvement in best corrected logMAR visual acuity at the Day 90 visit is an acceptable clinically relevant endpoint.*

Establishment of equivalence (comparing NGOIS to BSS PLUS) would require one adequate and well controlled clinical study but no additional claims other than those for which BSS PLUS is currently labeled could be made.

For efficacy and additional labeling claims, two adequate and well controlled clinical studies are required with a statistically significant difference (superiority) in a relevant clinical endpoint(s).

2. Clinical Protocol C-04-18 (Posterior Segment Study)

Alcon has modified the primary statistical objective of the protocol from a "describe" objective with provision of only descriptive statistics to an objective of demonstration of non-inferiority for NGOIS relative to BSS PLUS when used during surgery for removal of idiopathic epimacular membrane and vitrectomy. The test of non-inferiority will be performed for the proportion of patients with maintenance or improvement in best-corrected logMAR visual acuity at the Day 90 visit. A two-sided 95% confidence interval will be constructed for the difference between proportions in the two

treatments and non-inferiority will be declared if the lower confidence limit (LCL) for the difference in proportions (NGOIS – BSS PLUS) is greater than –20%. Primary inference for non-inferiority will be based on the per protocol (PP) data set. Does the Agency agree that this is an acceptable statistical plan?

Response: *See previous comments regarding the primary efficacy variable. A two-sided 95% confidence interval should be constructed for the difference between proportions in the two treatments and non-inferiority should be declared if the lower confidence limit (LCL) for the difference in proportions (NGOIS – BSS PLUS) is greater than –10%, not –20%.*

3. Clinical Protocol C-04-18 (Posterior Segment Study)

Alcon intends to use BSS PLUS as the active control for C-04-18 as previously stated in the request for Special Protocol Assessment for C-04-18 on December 1, 2004. Alcon is seeking clarification that BSS PLUS is an appropriate control for C-04-18 since the responses from the Agency to Alcon's request for a Special Protocol Assessment included ambiguous information on control groups for this study. The response to the first question indicated that BSS PLUS was appropriate, but question 10 indicated that a vehicle should be used for future trials. Does the Agency agree that BSS PLUS is an appropriate control group for C-04-18 rather than a vehicle?

Response: *For an appropriate control group for C-04-18, either the NGOIS should be superior to vehicle or be equivalent to BSS PLUS.*

4. Clinical Protocol C-04-18 (Posterior Segment Study)

Electroretinograms (ERG) will be collected at Baseline and at Day 90 post-operative in the surgical and fellow eyes. ERG is a specialized clinical measure with limited published data concerning normal ranges following removal of epimacular membrane and vitrectomy. Therefore, we propose conducting this evaluation as a pilot assessment. Data will be collected at 3 investigational sites that have access to ERG equipment and qualified personnel trained to use and interpret the results. Does the Agency agree that 3 investigational sites involving approximately 60 total patients (40 exposed to NGOIS and 20 exposed to BSS PLUS) are sufficient for this assessment?

Response: *Three (3) investigational sites involving approximately 60 total patients are acceptable as a pilot assessment.*

5. Clinical Protocol C-04-64 (Pediatric Study)

Since the Agency has advised Alcon in the End of Phase 2 Meeting minutes that "The Agency is not aware that there is a difference in clinical safety and efficacy between the adult and pediatric population...", we propose a total of 10 pediatric patients (at least 1 week old but less than 18 years old) be exposed to NGOIS with 10 BSS PLUS control patients in a cataract extraction study using phacoemulsification and posterior chamber IOL implantation. Does the Agency agree that this is an acceptable number of patients and study design?

Response: *Agree. A total of 10 pediatric patients (at least 1 week old but less than 18 years old) is an acceptable number of patients.*

6. Does the Agency agree that the performed and planned clinical studies will be sufficient to meet the requirements for the pediatric rule?

Response: *Agree.*

7. Does the Agency have any other advice concerning our development of NGOIS that the Agency believes is important in ensuring the filability of our proposed NDA?

Response: *Refer to response to question 1.*

The Division noted no other specific comments.

Minutes created by Lori Gorski, Project Manager
Concurred by Wiley A. Chambers, M.D

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Janice Soreth
6/16/05 04:08:12 PM

The following draft minutes were faxed to the sponsor on May 12, 2004 after our internal pre-meeting. As a result of receiving these comments Alcon decided that the May 17, 2004 EOP2 meeting was not longer needed and the meeting was cancelled.

DRAFT MEETING MINUTES TO THE SPONSOR

Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products

Meeting Date: May 17, 2004 Time: 11:00 AM EST

Application: IND 64,320 Meeting Type: EOP2

Drug: ~~XXXXXXXXXX~~ Intraocular Irrigating Solution b(4)

Sponsor: Alcon

These draft comments are being given to as a courtesy prior to our formal meeting on May 17. If you understand our responses and feel they warrant no further discussion, the May 17 meeting could be cancelled. If you do wish to still have the May 17th meeting, please remember we will not entertain any new questions or documentation for that meeting. If you wish to discuss any new information another meeting request should be submitted.

MEETING OBJECTIVES: Alcon is requesting guidance to advance to the Phase 3 trials.

b(4)

BACKGROUND INFORMATION: This document serves to inform the Division as to Alcon's development plans for ~~XXXXXXXXXX~~ Intraocular Irrigating Solution. Alcon's intent is to develop ~~XXXXXXXXXX~~ as an intraocular irrigating solution for use in the anterior and posterior segments during intraocular surgical procedures involving perfusion of the eye.

QUESTIONS

Chemistry, Manufacturing and Controls

1. The tests and specifications for ~~XXXXXXXXXX~~ Part I and the specifications for reconstituted product are listed in the Finished Product Section 2.3.P (see Table 2.3.P.5.1-1, Table 2.3.P.5.2-1 and Table 2.3.P.5.1-3). These parameters were developed based upon the current tests and specifications for Alcon's BSS PLUS[®] Part I. Since viscosity is an integral part of this new formulation, Alcon has added additional tests and specifications for hypromellose (HPMC) and for viscosity. For ~~XXXXXXXXXX~~ Part II, which is the same formulation as BSS PLUS[®] Part II, it is Alcon's intention to utilize the tests and specifications currently approved for that marketed product (see Table 2.3.P.5.1-2 and Table 2.3.P.5.2-2). Does the Division agree that the drug product tests and specifications are sufficient to provide appropriate control of the drug product?

b(4)

b(4)

Response: The acceptance criteria will be evaluated during the NDA review to reflect actual data. Impurities testing are recommended. The particulate matter criteria should be the same for both Part II and Part I, using the Part I criteria.

Nonclinical Safety

1. The information provided in the Toxicology Summary (section 2.4.3.) has been previously submitted as part of the original IND for [redacted] (IND 64,320), with the exception of the referenced rat reproduction/development study (section 2.4.3.7.; page 35), and the referenced intravitreal retention study (section 2.4.3.9.3.; page 38). Alcon believes that the nonclinical data package summarized in section 2.4.3 should be sufficient to support the NDA for [redacted] as an intraocular irrigating solution for use in the anterior and posterior segments during intraocular surgical procedures involving perfusion of the eye. Does the Division agree? b(4)

Response: The nonclinical package appears adequate for the NDA submission.

Clinical

Table 2.1-1 provides a summary of the overall clinical development plan for [redacted] including the studies completed to date and those Alcon plans to conduct. The clinical questions Alcon would like to have addressed are listed following Table 2.1-1. b(4)

1. The tables provide a summary of the IOP data for the post-surgical 6 hour visit from C-02-39 (page 70) and C-03-33 (page 82) which were conducted without the use of prophylactic IOP-reducing medications. Based on the 3 cps solution having an acceptable IOP profile while still maintaining efficacy (as indicated by the statistically significant reduction in turbulence), does the Division support our selection of [redacted] 3 cps for further development? b(4)

Response: The Agency cannot support any of the formulations of [redacted] at this time since safety will need to be evaluated in the context of the efficacy that is demonstrated. There does not appear to be a meaningful difference between any of the treatment groups in mean post-op IOP at any measured timepoint b(4)

2. In both C-02-39 and C-03-33, [redacted] demonstrated a statistically significant reduction in turbulence compared to BSS Plus. Therefore, in the proposed safety and efficacy study (C-04-14; page 63), Alcon proposes using turbulence as compared to BSS PLUS as the primary efficacy endpoint with the statistical objective of demonstrating superiority in turbulence ratings. Does the Division agree with this proposed endpoint and the statistical objective? b(4)

Response: The clinical utility of any claim will need to be established. The endpoint should be based on the claims proposed. Possible endpoints which could demonstrate effectiveness include improvement of post-op visual acuity, reduction in the number of intraoperative complications or a reduction in the number of instrument passes. At this time, "turbulence" could only be used as a claim and an endpoint if its clinical significance is known. The sponsor would need to submit existing data to the Agency that validate its clinical significance.

3. In Protocol C-04-14, Alcon plans to conduct postoperative visits at 6 hours, Day 1, Day 7, Day 30 and Day 90. This schedule is the same as the previous studies, with the exception that Alcon proposes to delete the Day 3 visit which was added to the initial studies to more closely monitor postoperative IOP

values. Alcon believes it is not necessary to include a Day 3 visit for the following reasons. During studies C-02-39 and C-03-33 no patients required initiation of IOP-reducing therapy at Day 3. There were only two patients who required additional therapy or a change in therapy at Day 3, and this was due to complications experienced during surgery. All other patients requiring therapy to reduce intraocular pressure received medication or manipulation of the wound at the 6 hour or Day 1 visit and were followed at the discretion of the investigator. Therefore, Alcon believes that requiring all patients to return for an additional post-operative visit on Day 3 is not necessary to ensure patient safety. Does the Division agree that the deletion of the Day 3 visit is acceptable?

Response: *Disagree. Patient 3105 had an elevated IOP (37 mmHg) at Day 3 after having all previous IOPs less than 30. Patient 2107 had an elevated IOP (37 mmHg) at Day 3 after having all previous IOPs less than 30.*

4. Studies C-02-39 and C-03-33 were performed without prophylactic IOP-reducing medications and planned study C-04-14 intends to use this same study design. Does the Division agree that this plan is acceptable?

Response: *Acceptable.*

5. In addition to the two completed studies (C-02-39 and C-03-33), Alcon proposes conducting two additional clinical trials for approval of _____ for intraocular surgical procedures: one anterior segment safety and efficacy study (C-04-14) and one posterior segment safety study (C-04-18). Are the number of studies, proposed study designs, and number of patients proposed (329 patients) in the Clinical Development Plan adequate for supporting the fileability of _____ for the indication for use as an intraocular irrigating solution during surgical procedures involving perfusion of the eye? b(4)

Response: *A fileability determination can not be made at this time. This decision will be made within 60 days of NDA submission.* b(4)

And the time of NDA filing, the Agency expects to see replicative studies demonstrating efficacy in a clinically meaningful endpoint. (see answers to questions 1 & 2).

6. In order to qualify _____ for use in posterior segment surgery, Alcon proposes to conduct a safety study in patients undergoing removal of idiopathic epiretinal membrane with vitrectomy compared to BSS PLUS utilizing 30 patients per arm (C-04-18; page 65). Safety will be assessed using several parameters, including electroretinogram, IOP, and dilated fundus exam. Does the Division agree that these study parameters are acceptable to assess safety for posterior segment surgery?

Response: *The study parameters appear acceptable based on the outline submitted. The Agency will need to review the protocol before giving full concurrence.*

7. Alcon proposes that the total patient exposure number should include the 70 patients treated with the ~~_____~~ 5 cps solution as this is a worse case exposure to drug. However, Alcon believes that the adverse events for this elevated concentration are not appropriate to include in the calculations for the "Adverse Reactions" section of the product labeling since the marketed product will be _____ 3 cps. Does the Division agree with this proposal? b(4)

Response: A decision on product labeling will be made after review of the NDA. 21 CFR 201.57(g) states the labeling shall list the adverse reactions that occur with the drug and with drugs in the same pharmacologically active and chemically related class. Alternative concentrations are therefore applicable.

Other

1. Alcon's medical advisors have informed us that they believe that there are no different issues of safety and efficacy in use of ~~_____~~ in pediatric patients than in adults. Does the Division have any comments, at this time, concerning the need for pediatric studies and whether the pediatric effectiveness of ~~_____~~ can be extrapolated from Alcon's adult studies C-03-33 (completed), C-04-14 (planned anterior segment study) and C-04-18 (planned posterior segment study)?

b(4)

Response: The Agency is not aware that there is a difference in clinical safety and efficacy between the adult and pediatric population and therefore encourages the inclusion of pediatric patients in the clinical trials.

2. Does the Division have any other advice concerning our development of ~~_____~~ Intraocular Irrigating Solution that the Division believes is important in ensuring the fileability of our proposed NDA?

b(4)

Response: See responses to questions 1 & 2.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Lori Gorski
6/17/04 08:53:13 AM
CSO

Wiley Chambers
6/17/04 05:21:06 PM
MEDICAL OFFICER

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION		
NDA # 22-193 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: NavstelIntraocular Irrigating Solution Sterile Established/Proper Name: balanced salt ophthalmic solution with hypromellose, dextrose and glutathione Dosage Form: solution		Applicant: Alcon Inc. Agent for Applicant (if applicable): Alcon Research Ltd.
RPM: Lori Gorski		Division: Division of Anti-Infective and Ophthalmology Products
<p>NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p>		<p>505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> If no listed drug, check here and explain:</p> <p>Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.</p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p> <p>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</p>
❖ User Fee Goal Date Action Goal Date (if different)		July 24, 2008
❖ Actions		
• Proposed action		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
• Previous actions (specify type and date for each action taken)		<input checked="" type="checkbox"/> None
❖ Advertising (approvals only) Note: If accelerated approval (21 CFR 314.510/601.41), advertising MUST have been submitted and reviewed (indicate dates of reviews)		<input checked="" type="checkbox"/> Requested in AP letter <input type="checkbox"/> Received and reviewed

The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

Application² Characteristics

Review priority: Standard Priority
 Chemical classification (new NDAs only): 3

- Fast Track
- Rolling Review
- Orphan drug designation

- Rx-to-OTC full switch
- Rx-to-OTC partial switch
- Direct-to-OTC

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
- Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR
- Submitted in response to a PMC

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
- Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

Comments:

❖ Application Integrity Policy (AIP) http://www.fda.gov/ora/compliance_ref/aip_page.html

- Applicant is on the AIP

Yes No

- This application is on the AIP

Yes No

- If yes, exception for review granted (*file Center Director's memo in Administrative/Regulatory Documents section, with Administrative Reviews*)
- If yes, OC clearance for approval (*file communication in Administrative/Regulatory Documents section with Administrative Reviews*)

Yes

Yes Not an AP action

- ❖ Date reviewed by PeRC (*required for approvals only*)
 If PeRC review not necessary, explain:

April 23, 2008

- ❖ BLAs only: *RMS-BLA Product Information Sheet for TBP* has been completed and forwarded to OBPS/DRM (*approvals only*)

Yes, date

- ❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 (*approvals only*)

Yes No

❖ Public communications (*approvals only*)

- Office of Executive Programs (OEP) liaison has been notified of action
- Press Office notified of action

Yes No

Yes No

- Indicate what types (if any) of information dissemination are anticipated

- None
- HHS Press Release
- FDA Talk Paper
- CDER Q&As
- Other

² All questions in all sections pertain to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLA: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification. 	<input type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? (Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.) 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date 10-year limitation expires: _____
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input type="checkbox"/> No paragraph III certification Date patent will expire _____
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). (If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)). 	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for each paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).

If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.

CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist³

included

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (*approvals only*)

Included

Documentation of consent/nonconsent by officers/employees

Included

Action Letters

❖ Copies of all action letters (*including approval letter with final labeling*)

Action(s) and date(s) AP
July 24, 2008

Labeling

❖ Package Insert (*write submission/communication date at upper right of first page of PI*)

❖ Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)

in AP letter

❖ Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)

July 23, 2008

❖ Original applicant-proposed labeling

yes

❖ Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable

❖ Medication Guide/Patient Package Insert/Instructions for Use (*write submission/communication date at upper right of first page of each piece*)

Medication Guide
 Patient Package Insert
 Instructions for Use
 None

❖ Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)

³ Fill in blanks with dates of reviews, letters, etc.

❖ Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	
❖ Original applicant-proposed labeling	
❖ Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Labels (full color carton and immediate-container labels) (write submission/communication date at upper right of first page of each submission)	
❖ Most-recent division proposal for (only if generated after latest applicant submission)	
❖ Most recent applicant-proposed labeling	
❖ Labeling reviews (indicate dates of reviews and meetings)	<input type="checkbox"/> RPM <input type="checkbox"/> DMEDP <input type="checkbox"/> DRISK <input checked="" type="checkbox"/> DDMAC 3/28/08 <input type="checkbox"/> CSS <input checked="" type="checkbox"/> Other reviews DMETS 3/18/08
Administrative/Regulatory Documents	
❖ Administrative Reviews (e.g., RPM Filing Review ⁴ /Memo of Filing Meeting) (indicate date of each review)	
❖ NDAs only: Exclusivity Summary (signed by Division Director)	<input type="checkbox"/> Included
❖ AIP-related documents <ul style="list-style-type: none"> • Center Director's Exception for Review memo • If approval action, OC clearance for approval 	<input checked="" type="checkbox"/> Not on AIP
❖ Pediatric Page (approvals only, must be reviewed by PERC before finalized)	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (include certification)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Postmarketing Requirement (PMR) Studies <ul style="list-style-type: none"> • Outgoing communications (if located elsewhere in package, state where located) • Incoming submissions/communications 	<input checked="" type="checkbox"/> None
❖ Postmarketing Commitment (PMC) Studies <ul style="list-style-type: none"> • Outgoing Agency request for postmarketing commitments (if located elsewhere in package, state where located) • Incoming submission documenting commitment 	<input checked="" type="checkbox"/> None
❖ Outgoing communications (letters (except previous action letters), emails, faxes, telecons)	in package
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• Pre-Approval Safety Conference (indicate date; approvals only)	<input checked="" type="checkbox"/> Not applicable
• Regulatory Briefing (indicate date)	<input checked="" type="checkbox"/> No mtg
• Pre-NDA/BLA meeting (indicate date)	<input checked="" type="checkbox"/> No mtg
• EOP2 meeting (indicate date)	<input type="checkbox"/> No mtg May 17, 2004
• Other (e.g., EOP2a, CMC pilot programs)	SPA June 16, 2005

⁴ Filing reviews for other disciplines should be filed behind the discipline tab.

Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None July 24, 2008
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Information	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	NA
• Clinical review(s) (<i>indicate date for each review</i>)	July 24, 2008
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Safety update review(s) (<i>indicate location/date if incorporated into another review</i>)	in review
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	in clin review
❖ Clinical reviews from other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not needed
❖ REMS	<input checked="" type="checkbox"/> None
• REMS Document and Supporting Statement (<i>indicate date(s) of submission(s)</i>)	
• Review(s) and recommendations (including those by OSE and CSS) (<i>indicate location/date if incorporated into another review</i>)	
❖ DSI Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input type="checkbox"/> None requested
• Clinical Studies	July 3, 2008
• Bioequivalence Studies	NA
• Clinical Pharmacology Studies	NA
Clinical Microbiology	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Biostatistics	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Statistical Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None

⁵ Filing reviews should be filed with the discipline reviews.

Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None March 20, 2008
DSI Clinical Pharmacology Inspection Review Summary	<input checked="" type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Supervisory Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None April 8, 2008
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary	<input checked="" type="checkbox"/> None requested
CMC/Quality <input type="checkbox"/> None	
❖ CMC/Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Branch Chief/TeamLeader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• CMC/product quality review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None February 28,2008
• BLAs only: Facility information review(s) <i>(indicate dates)</i>	<input checked="" type="checkbox"/> None
❖ Microbiology Reviews	
• NDAs: Microbiology reviews (sterility & pyrogenicity) <i>(indicate date of each review)</i>	July 2, 2008 <input type="checkbox"/> Not needed
• BLAs: Sterility assurance, product quality microbiology	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	CMC review
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Facilities Review/Inspection	
• NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date)</i>	Date completed: April 28, 2008 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
• BLAs:	
➤ TBP-EER	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
➤ Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) <i>(date completed must be within 60 days prior to AP)</i>	Date completed: <input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold

NDA: Methods Validation

- Completed
- Requested
- Not yet requested
- Not needed

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.