

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-308**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 22-308

SUPPL #

HFD #

Trade Name BESIVANCE

Generic Name besifloxacin hydrochloride ophthalmic suspension

Applicant Name Bausch & Lomb Incorporated

Approval Date, If Known TBD

### 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?

Five

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#

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:

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

Explain:

!

!

! NO

! Explain:

Investigation #2

YES

Explain:

!

!

! NO

! 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:

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Name of person completing form: Alison Rodgers

Title: Regulatory Health Project Manager

Date: February 17, 2009

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

Title: Acting Director, Division of Anti-Infective and Ophthalmology Products

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

**PEDIATRIC PAGE**  
**(Complete for all filed original applications and efficacy supplements)**

NDA/BLA#: 22-308 Supplement Number: \_\_\_\_\_ NDA Supplement Type (e.g. SE5): \_\_\_\_\_

Division Name: Anti-Infective and Ophthalmology Products PDUFA Goal Date: 4-2-09 Stamp Date: 6/2/2008

Proprietary Name: BESIVANCE

Established/Generic Name: besifloxacin hydrochloride ophthalmic suspension

Dosage Form: Topical Ophthalmic

Applicant/Sponsor: Bausch & Lomb Incorporated

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

- (1) None  
(2) \_\_\_\_\_  
(3) \_\_\_\_\_  
(4) \_\_\_\_\_

**Q1:** Is this application in response to a PREA PMC? Yes  Continue  
No  Please proceed to Question 2.

If Yes, NDA/BLA#: \_\_\_\_\_ Supplement #: \_\_\_\_\_ PMC #: \_\_\_\_\_

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

- Yes. **Skip to signature block.**  
 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);  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.**

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:** bacterial conjunctivitis

**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 the remaining 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)

**IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL OR AT 301-796-0700.**

(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)

- 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 ineffective or 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 and entered into DFS.

**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 <sup>#</sup>	Not meaningful therapeutic benefit <sup>*</sup>	Ineffective or unsafe <sup>†</sup>	Formulation failed <sup>Δ</sup>
<input checked="" type="checkbox"/>	Neonate	0 wk. __ mo.	__ wk. 1 mo.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input checked="" type="checkbox"/>	Other	__ yr. 1 mo.	__ yr. 12 mo.	<input checked="" 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 under the 1 month
  - Too few children with disease/condition to study between 1 month and 1 year of age
  - 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 ineffective or unsafe in this/these pediatric population(s) (Note: if studies are partially waived on this ground, this information must be included in

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL OR AT 301-796-0700.

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 F and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Sections D and F and complete the PeRC Pediatric Assessment form); and/or (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 Sections E and F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

**Section C: Deferred Studies (for remaining pediatric subpopulations). Complete Section F on Extrapolation.**

Check pediatric subpopulation 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)*	Yes	No	
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<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"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<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"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<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"/>	<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-

**IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL OR AT 301-796-0700.**

marketing commitment.)

If all of the pediatric subpopulations have been covered through the partial waivers and deferrals, proceed to Section F. For those pediatric subpopulations for which studies have been completed, proceed to Sections D and F and complete the PeRC Pediatric Assessment form. For those pediatric subpopulations for which additional studies are not needed because the drug is appropriately labeled in one or more pediatric subpopulations, proceed to Sections E and F.

**Section D: Completed Studies (for some or all pediatric subpopulations). Complete Section F on Extrapolation.**

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input checked="" type="checkbox"/>	Other	1 yr. __ mo.	16 yr. 11 mo.	Yes <input checked="" 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"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input 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: For those pediatric subpopulations for which additional studies are not needed because the drug is appropriately labeled in one or more pediatric subpopulations, proceed to Sections E and F. If there are no further pediatric subpopulations to cover based on the partial waivers, deferrals and completed studies, go to Section F.

**Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations): (Complete section F)**

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 studies are not needed because efficacy is being extrapolated from other adult and/or pediatric studies, proceed to Section F. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS.

**IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL OR AT 301-796-0700.**

**Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and 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 target pediatric subpopulation needing studies. 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 pharmacokinetic and safety studies.*

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"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input checked="" 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.*

This page was completed by:

{See appended electronic signature page}

\_\_\_\_\_  
Acting Division Director

(Revised: 4/2008)

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700**

(Revised: 4/2008)

**IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL OR AT 301-796-0700.**

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

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Wiley Chambers  
5/22/2009 09:32:12 AM

**1.3.3 Debarment Certification**

Bausch & Lomb Incorporated hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

  
\_\_\_\_\_  
Jennifer S. Knicley  
Manager, Regulatory Affairs

5/19/2008  
Date

MEMORANDUM

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

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**AMENDED CLINICAL INSPECTION SUMMARY**

(Amended to include results of CI inspection for Penny Asbell, M.D.)

DATE: 05-22-2009

TO: Alison Rodgers, Regulatory Project Manager  
Martin Nevitt, M.D., Medical Officer  
Division of Anti-Infective and Ophthalmic Products

FROM: Jean Mulinde, M.D.  
Good Clinical Practice Branch 2  
Division of Scientific Investigations

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

SUBJECT: Evaluation of Clinical Inspections.

NDA: 22-308

APPLICANT: Bausch & Lomb Incorporated

DRUG: Optura™ (besifloxacin hydrochloride ophthalmic suspension, 0.6%  
as base)

NME: Yes

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATIONS: 1. Treatment of bacterial conjunctivitis

CONSULTATION REQUEST DATE: 07/18/2009

DIVISION ACTION GOAL DATE: 04/02/2009

PDUFA DATE: 04/02/2009

## I. BACKGROUND:

Optura™ (besifloxacin hydrochloride ophthalmic suspension, 0.6% as base) is a new molecular entity that belongs to the class of fluoroquinolone anti-infectives. Its mechanism of action involves the inhibition of both bacterial DNA gyrase and topoisomerase IV. Based on *in vitro* microbiologic data, besifloxacin is predicted to have clinical efficacy against aerobic, facultative, and anaerobic Gram-positive and Gram-negative bacteria, including those common pathogens causing bacterial conjunctivitis (e.g., *Staphylococcus aureus*, *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Corynebacter* species, and *Moraxella* species). In NDA 22-308, the Applicant (Bausch & Lomb Inc.) has requested that besifloxacin hydrochloride ophthalmic suspension be approved for the treatment of bacterial conjunctivitis. To support approval, the Applicant has provided data from three pivotal clinical trials (Protocol #373, Protocol #433, and Protocol #434), which they believe provide sufficient evidence for the safety and efficacy of besifloxacin dosed three times daily for 7 days for proposed indication.

The protocols inspected include:

1. Protocol #373: A Study to Evaluate the Clinical and Microbial Efficacy of 0.6% ISV-403 Compared to Vehicle in the Treatment of Bacterial Conjunctivitis

This study was a multicenter, randomized, double-masked, parallel Phase 2 trial conducted at 35 centers in the United States. Patients were to receive either 0.6% ISV-403 (besifloxacin) chloride or ISV-403 vehicle to be instilled to infected eye(s) as one drop at 6-hour intervals (3 times a day) for 5 days. Patients were enrolled in the study from December 28, 2004 through June 7, 2005 (Date of final study report: April 4, 2008).

The primary efficacy endpoints of this study were clinical resolution and eradication of baseline bacterial infection at Visit 3 (study Day 8 +1 day). Clinical resolution was defined as the absence of the following three clinical signs: conjunctival discharge, bulbar conjunctival injection, and palpebral conjunctival injection. All subjects who were randomly assigned to treatment and that had bacteriologically confirmed conjunctivitis were evaluated for the primary endpoints in the intent-to-treat analyses. Key secondary endpoints were:

- individual signs and symptoms
- investigator global ratings
- microbiological and clinical outcome rates on a 0 to 3 scale.

Safety measurements included adverse events, visual acuity changes, biomicroscopy evaluations and ophthalmoscopy.

2. Protocol #433: A Study to Evaluate the Clinical and Microbial Efficacy of 0.6% ISV-403 Compared to Vehicle in the Treatment of Bacterial Conjunctivitis

This study was a multicenter, randomized, double-masked, vehicle-controlled, parallel-group Phase 3 trial conducted at 58 centers in the United States. Patients were to receive besifloxacin Hydrochloride Ophthalmic Suspension, 0.6% as a base (besifloxacin) or vehicle suspension instilled in infected eye(s) as one drop 3 times a day for 5 days.

Patients were enrolled in the study from June 5, 2006 through November 7, 2007 (Date of final study report: April 8, 2008).

The primary efficacy endpoints of this study were clinical resolution and eradication of baseline bacterial infection at Visit 2 (study Day 5  $\pm$ 1 day). Clinical resolution was defined as the absence of the following two clinical signs: ocular discharge, and bulbar conjunctival injection. All subjects who were randomly assigned to treatment and that had bacteriologically confirmed conjunctivitis were evaluated for the primary endpoints in the intent-to-treat analyses. Key secondary endpoints were:

- clinical resolution at Day 8, as defined for the primary endpoint
- microbial eradication of baseline infection at Day 8
- individual signs and symptoms at each follow-up visit

Safety measurements included adverse events, visual acuity changes, biomicroscopy evaluations and ophthalmoscopy.

3. Protocol #434: A Study to Evaluate the Clinical and Microbial Efficacy of 0.6% ISV-403 Compared to Vigamox in the Treatment of Bacterial Conjunctivitis

This study was a multicenter, randomized, double-masked, active-controlled, parallel-group Phase 3 trial conducted at 84 centers in the United States and Asia. Patients were to receive either besifloxacin Hydrochloride Ophthalmic Suspension, 0.6% as a base (besifloxacin) or Vigamox (moxifloxacin hydrochloride ophthalmic solution) instilled in infected eye(s) as one drop 3 times a day for 5 days. Patients were enrolled in the study from June 6, 2006 through July 13, 2007 (Date of final study report: March 28, 2008).

The primary efficacy endpoints of this study were clinical resolution and eradication of baseline bacterial infection at Visit 2 (study Day 5  $\pm$ 1 day). Clinical resolution was defined as the absence of the following two clinical signs: ocular discharge, and bulbar conjunctival injection. All subjects who were randomly assigned to treatment and that had bacteriologically confirmed conjunctivitis were evaluated for the primary endpoints in the intent-to-treat analyses. Key secondary endpoints were:

- clinical resolution at Day 8, as defined for the primary endpoint
- microbial eradication of baseline infection at Day 8
- individual signs and symptoms at each follow-up visit

Safety measurements included adverse events, visual acuity changes, biomicroscopy evaluations and ophthalmoscopy.

Four clinical investigators, each of whom contributed large numbers of subjects to the study that they participated in and that were noted to have large numbers of protocol deviations reported in the NDA, were chosen for FDA PDUFA inspections. As the product was a new molecular entity an inspection of the Sponsor was also conducted. In addition, the Final Study Reports contained in NDA 22-308 identified a number of clinical investigators (CI) that had been terminated as CIs from studies early by the sponsor as a result of "continued major GCP non-compliance" and DSI determined that FDA For Cause/PDUFA inspections were indicated at two of these CI sites. The reasons that Bausch & Lomb Incorporated terminated these two sites are summarized below (from General Communication to IND 64, 335, Serial 0060, dated

June 5, 2008):

- Protocol #433 Noli R. Zosa, M.D. - Site failed to follow visit window and subject eligibility requirements (e.g. ocular discharge was absent at time to enrollment), investigator demonstrated a general lack of understanding of protocol requirements and awareness of GCP.
- Protocol #434 Penny Asbell, M.D. - Site randomized subjects incorrectly, failed to follow visit window requirements and proper bacterial culture techniques (e.g. cultures shipped under improper conditions); in addition to inadequate investigator supervision of study and informed consent process overall.

**II. RESULTS (by Site):**

Name of CI, IRB, or Sponsor Location	Protocol # Site # # of Subjects	Inspection Date	Final Classification
Lee E. Rigel, O.D. VisionCare Associates 310 W. Lake Lansing Rd. Lansing, MI 48823	Protocol #373 Site #033 30 Subjects	09/08/2008- 09/11/2008	VAI
Warren H. Heller, M.D. Arizona Center for Clinical Trials 515 W. Buckeye Rd, #206 Phoenix, AZ 85003	Protocol #433 Site #725416 78 Subjects	09/11/2008- 09/15/2008	NAI
Bruce E. Kanengiser, M.D. Clinical Research Laboratories, Inc. 371 Hoes Lane Piscataway, NJ 08854 USA	Protocol #433 Site #700440 71 Subjects	08/26/2008- 09/24/2008	VAI
Noli R. Zosa, M.D. 8337 Telegraph Road, Suite 125A Pico Rivera, CA 90660	Protocol #433 Site #691449 4 Subjects	10/02/2008- 10/07/2008	Pending (Preliminary classification OAI)
Buhilda McGriff, M.D. Carolina Pediatric Eye Specialists 992 Copperfield Blvd Concord, NC 28025	Protocol #434 Site #750393 52 Subjects	08/28/2008- 09/04/2008	VAI
Penny A. Asbell, M.D. 100 <sup>th</sup> Street & Madison Ave Annennberg Bldg 22 Floor, Suite22 New York, NY 10029	Protocol #434 Site #748395 6 Subjects	02/05/2009- 02/24/2009	VAI
Bausch & Lomb Incorporated 1400 North Goodman Street Rochester, NY 14609	NDA #22-308 Protocol #373 Protocol #433 Protocol #434	09/02/2008- 09/05/2008	VAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary, letter has not yet issued to the CI.

1. **Lee Rigel, OD**

VisionCare Associates  
310 W. Lake Lansing Rd.  
Lansing, MI 48823  
Protocol #373, Site #033

a. **What was inspected:**

This inspection was conducted in accordance with Compliance Program 7348.811 between 09/08/2008-09/11/2008. A total of 30 subjects were screened, 30 subjects were enrolled and 27 completed the study. Three subjects were withdrawn due to insufficient therapeutic response. Records for all 30 subjects were reviewed to verify that eligibility criteria were met, that all data in CRFs matched source documents and line listings, and that informed consents and assents were appropriately completed. In addition, drug accountability records, IRB approval and dates, and sponsor monitoring records were reviewed. There were no limitations to the inspection.

b. **General observations/commentary:**

The inspection of Dr. Rigel's site revealed regulatory violations. A Form FDA 483, Inspectional Observations, was issued to this investigator for failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the inspection. [21 CFR 312.62 (b)] The specific observations included failure to completely document the timing of and personnel administering pregnancy tests and failure to document the method of birth control by several subjects of child-bearing potential.

c. **Assessment of data integrity:**

Although a regulatory violation was noted, it is unlikely that it significantly affects overall reliability of safety and efficacy data from the site. Based on the provided Establishment Inspection Report (EIR) for this site, data derived from Dr. Rigel's site are considered acceptable.

2. **Warren H. Heller, MD**

Arizona Center for Clinical Trials  
515 W. Buckeye Rd, #206  
Phoenix, AZ 85003  
Protocol #433, Site #725416

a. **What was inspected:**

This inspection was conducted in accordance with Compliance Program 7348.811 between 09/11/2008-09/15/2008. A total of 79 subjects were screened, 78 subjects were enrolled and 69 completed the study. Records for 20 subjects were reviewed to verify that eligibility criteria were met, that all data in CRFs matched source documents and line listings, and that informed consents

and assents, if indicated, were appropriately completed. In addition, drug accountability records, IRB approval and dates, and sponsor monitoring records were reviewed. There were no limitations to the inspection.

b. **General observations/commentary:**

The inspection of Dr. Heller's site did not reveal regulatory violations. A Form FDA 483, Inspectional Observations, was not issued.

c. **Assessment of data integrity:**

Based on the provided Establishment Inspection Report (EIR) for this site, data derived from Dr. Heller's site are considered acceptable.

3. **Bruce E. Kanengiser, MD**

Clinical Research Laboratories, Inc.  
371 Hoes Lane  
Piscataway, NJ 08854 USA  
Protocol #433, Site #700440

a. **What was inspected:**

This inspection was conducted in accordance with Compliance Program 7348.811 between 08/26/2008-09/24/2008. A total of 73 subjects were screened, 71 subjects were enrolled and 69 completed the study. During the inspection, 100% of the data were audited, (comparing the source record, eCRF, and data listings provided in the NDA) for subject eligibility criteria, clinical assessment and global change ratings, visual acuity results, direct ophthalmoscopy results, microbiologic results, concomitant medication use, study drug dispensing, adverse events, subject discontinuations, and protocol violations. Fifty percent of subject data were audited for biomicroscopy results. In addition, informed consent documents, drug accountability records, IRB approval and dates, and sponsor monitoring records were reviewed. There were no limitations to the inspection.

b. **General observations/commentary:**

The inspection of Dr. Kanengiser's site revealed regulatory violations. A Form FDA 483, Inspectional Observations, was issued to this investigator for:

- i. Failure to obtain informed consent in accordance with 21 CFR Part 50 from each human subject prior to drug administration. Specifically, for failing to obtain assent from four subjects (Subjects #0398, #0399, #0696, and #0800) between the ages to 6 and 11 years and failing to obtain consent from one subject (Subject #0523) between the age of 12 and 18 years as was required by the protocol and/or study plan.

**DSI Reviewer Comment:** DSI notes, however, that in each case informed consent documents were signed by the subjects' legally authorized

**representatives.**

- ii. Failure to ensure that all changes in research activity were approved by an Institutional Review Board (IRB) prior to implementation [21 CFR 312.66]. Specifically, for failing to obtain approval from the IRB prior to increasing enrollment numbers at the site and for failing to notify the IRB of actual enrollment of children in the study in 3 progress reports made to the IRB. While the protocol and consents originally approved by the IRB allowed enrollment of pediatric subjects, the site failed to accurately complete the section of required q6mo study status reports submitted that would inform them of the status of pediatric subject enrollment at the site.
- iii. Failure to provide updated financial information to the study sponsor when relevant changes occurred during the course of the investigation [21 CFR 312.64(d)]. Specifically, for failing to provide the sponsor with financial disclosure forms completed and signed by two foreign medical doctors who made a direct and significant contribution to the study data.

**DSI Reviewer Comment:** Based on DSI's review of the CI's response dated September 29, 2008, the CI has obtained and forwarded to the sponsor a completed financial disclosure form from one of these individuals. The second individual is no longer in his employ, but he has provided evidence that he has attempted to secure a completed financial disclosure form from this individual as well, though without success.

- iv. Failure to prepare or maintain accurate case histories with respect to observations and data pertinent to the investigation [21 CFR 312.62(b)]. Specifically, for incorrectly recording in the eCRF portions of Visit 1 biomicroscopy examinations (chemosis and/or hyperemia results) for six of thirty-six subjects (Subjects #0247, #0263, #0528, #0621, #0265, and #0619) audited. In each case source documents described the condition as 2=Mod or 1=Mild and the value recorded in the eCRF was 0=None.

Subject #	Visit	Eye	Condition	Degree (Source Document)	Degree (eCRF)
0247	1	OD	Chemosis	2=Mod	0=None
0247	1	OS	Chemosis	1=Mild	0=None
0263	1	OS	Hyperemia	1=Mild	0=None
0528	1	OD	Hyperemia	1=Mild	0=None
0528	1	OS	Hyperemia	1=Mild	0=None
0621	1	OD	Hyperemia	1=Mild	0=None
0621	1	OS	Hyperemia	1=Mild	0=None
0265	1	OD	Chemosis	1=Mild	0=None
0265	1	OS	Chemosis	1=Mild	0=None
0619	1	OS	Hyperemia	1=Mild	0=None
0619	1	OS	Chemosis	1=Mild	0=None

- v. Failure to ensure that the investigation was conducted according to the

signed investigator statement and the investigational plan [21 CFR 312.60]. Specifically for:

- a) Failing to list two sub-investigators on Form FDA 1572s submitted to the sponsor.
- b) Failing to adequately document that the CI was not present during instillation of in-office study medication drops during Visit 1 and/or Visit 2 study procedures. Statements were made in source documents for each subject that the CI was not present, but these statements were not signed, initialed, or dated by the individual making them in many cases.
- c) Storage conditions for study drug, as required by the protocol, were not documented for four of 33 weeks reviewed during the audit and storage temperatures fell outside of the protocol required storage at 59-77°F for a portion of 19 of 33 weeks audited. The upper bound temperature could not be ascertained because the needle used by the device appears to have run off the paper recording discs (highest temp on disc = 120°F).

**DSI Reviewer Comment:** Based on DSI's review of the EIR it seems unlikely that room temperature conditions would have reached temperatures as high as 120°F during the time periods recorded (October through April in New Jersey); therefore, DSI considers it likely that the findings are secondary to device malfunction. In the CI's response dated September 29, 2008, he has provided evidence that this device has subsequently been replaced to prevent further such occurrences in future studies.

- d) Failure to attempt to contact one subject that did not present for a required visit as was required in Section 8.5.4 of the protocol.
- vi. Failure to return unused supplies of an investigational drug to the sponsor [21 CFR 312.62(a)]. Specifically, the protocol required that all used and unused units of investigational material be returned to the sponsor, but documentation that the site was inadequate to assure that all used and unused units were returned Bausch & Lomb.

**DSI Reviewer Comment:** Based on DSI's review of the CI's response dated September 29, 2008, study monitors did document in monitoring reports that used and unused units were returned to the sponsor, but documentation was not specific as to kit numbers/vial numbers returned. While it appears likely that study drug was appropriately disposed of during and at the conclusion of the study, DSI considers site's lack of adequately detailed disposition records to be regulatory violation.

- c. Assessment of data integrity:

While multiple regulatory violations occurred at this site it does not appear that subject safety was compromised. Overall efficacy and safety data appear reliable with the exception of the data noted for the six subjects described in section iv.

4. **Noli R. Zosa, MD**

8337 Telegraph Road, Suite 125A  
Pico Rivera, CA 90660  
Protocol #433, Site #691449

a. **What was inspected:**

This inspection was conducted in accordance with Compliance Program 7348.811 between 10/02/2008-10/07/2008. A total of four subjects were screened, four subjects were enrolled and one appears to have completed the study. Two subjects were withdrawn from the study when study monitors determined that they did not meet eligibility criteria. Based on study documents available at the site, it could not be determined if the fourth subject completed the study. Available records for all subjects were reviewed. Records were limited to printed eCRF documents for 3 subjects and no source documentation was available to substantiate these subjects' existence and eligibility to participate in the study. For one subject both the eCRF and a patient chart were available, but there was no documentation of the subject's participation in the study in the patient's chart. A regulatory binder was available for review at the site that contained the following items for review: communications between the site and the IRB, a delegation of authority of clinical responsibilities for the study, CI Form FDA 1572s, a monitoring visit log, a test article accountability log, and communications from study monitors to the CI. The absence of study related source documents specific to enrolled subjects was a limiting factor for this inspection.

b. **General observations/commentary:**

The inspection of Dr. Zosa's site revealed regulatory violations. A Form FDA 483, Inspectional Observations, was issued to this investigator for:

- i. Failure to conduct the study according to the signed investigator statement and the investigational plan [21 CFR 312.60]. Specifically, for:

Three of four enrolled subjects did not meet study eligibility criteria. Subject #1054 and Subject #0155 did not have minimum scores required for ocular discharge and Subject #0156 was less than one year old.

- ii. Failure to obtain informed consent in accordance with 21 CFR Part 50 from each human subject prior to drug administration. Specifically for:

Signed informed consent documents were not present for any of the four subjects enrolled by the CI.

- iii. Failure to prepare or maintain adequate case histories with respect to observations and data pertinent to the investigation [21 CFR 312.62(b)]. Specifically for:

There were no source documents in the CI's records to corroborate entries made on the electronic case report forms for the clinical study for Study #433. Source documents not on file included: ophthalmologic assessments, visual acuity assessments, laboratory requisitions, subject medical charts, laboratory reports for collected specimens, subject diaries documenting daily drug administration, and documentation of pregnancy testing (when indicated).

- c. **Assessment of data integrity:**

There are multiple items listed on the Form FDA 483 and detailed in the EIR for this CI that raise serious concerns with data reliability and integrity at this site; therefore, DSI recommends that data from this site not be used to support approval of the NDA.

5. **Buhilda McGriff, MD**

Carolina Pediatric Eye Specialists  
992 Copperfield Blvd  
Concord, NC 28025  
Protocol #434, Site #750393

- a. **What was inspected:**

This inspection was conducted in accordance with Compliance Program 7348.811 between 09/08/2008-09/11/2008. A total of 58 subjects were screened, 52 subjects were enrolled and 48 completed the study. Records for 22 subjects were reviewed to verify that data recorded in NDA line listings and subjects' case report forms were the same as information documented in source records. A random review for adverse events revealed that all adverse events appear to have been appropriately reported. In addition, drug accountability records, IRB approval and dates, and sponsor monitoring records were reviewed. There were no limitations to the inspection.

- b. **General observations/commentary:**

The inspection of Dr. McGriff's site revealed regulatory violations. A Form FDA 483, Inspectional Observations, was issued to this investigator for:

- i. Failure to obtain informed consent in accordance with 21 CFR Part 50 from each human subject prior to drug administration. Specifically for:
  - a) Conduct of study related procedures and dosing of two subjects (Subject #0406 and Subject #0407) occurred prior to their signing the study informed consent document.

- b) Written informed consent not being properly documented in that written informed consent was not appropriately completed by either the subject or their legally authorized representative and/or by the individual conducting the informed consent discussion for five subjects. Observations included signing of informed consent by individual conducting the informed consent discussion at a date after the informed consent was signed by subjects in four cases (Subject #0045, Subject #0406, Subject #0407, and Subject #1015) and that subjects signed some, but not all places required in the informed consent document (Subject #0045, Subject #0406, and Subject #1014).
  - c) Study Assent Forms were to have been signed only by subjects between the ages of 6 to 11 years. Assent Forms were also signed, by the subject or by their legally authorized representative, for at least 15 subjects that were less than 6 years of age or greater than 11 years of age.
- iv. Failure to conduct the study according to the signed investigator statement and the investigational plan [21 CFR 312.60]. Specifically, for:
- a) Failure to conduct study visits between the hours of 7am and 10am for two subjects as specified by the protocol (Subject #0045 Visit 3 and Subject #0407 Visit 2).
  - b) Subjects were not to self administer study drug on the morning of study visit 2. This dose was to be administered at the CI site after the visit 2 assessment and eye culture. Five subjects, however, administered a dose of study drug in the AM prior to visit 2 (Subjects #0406, #0407, #0828, #1152, and #1231).
  - c) The protocol stated that study medication was to be instilled in the infected eye three times a day for Day 1 to Day 5 of the study. Four subjects did not administer doses according to this regimen. Subject #0406 and Subject #0407 continued to use study medication Days 6, 7, and 8. Subject #1085 and Subject #1086 missed two doses on Day 5 and continued to use study medication on Days 6, 7, and 8.
- c. **Assessment of data integrity:**  
 Although regulatory violations were noted in i) a) above, it is unlikely that they significantly affect overall reliability of safety and efficacy data from the site. Observations included in i) b) are not considered valid regulatory violations as the FDA does not have the regulatory authority to require signature of HIPPA related documents or to require that informed consent documents be witnessed (other than as specified for emergency use). Item i) c), while factual, does not impact the reliability of data submitted by this site. Regarding the protocol deviations noted for subjects in ii) above, it appears that the Sponsor appropriately excluded these subjects from the per protocol analyses in the NDA submission. The data is considered acceptable from this site.

6. **Penny A. Asbell, MD**  
100th Street & Madison Ave  
Annennberg Bldg 22 Floor, Suite22  
New York, NY 10029  
Protocol #434, Site #748395

a. **What was inspected:**

This inspection was conducted in accordance with Compliance Program 7348.811 between 02/05/2009 and 02/24/2009. This inspection was performed as a data audit for NDA #22-308 as a result of the Applicant identifying in the Study Report for Study #434 that this site had been closed during the study due to concerns with GCP violations. A total of six subjects were screened, six subjects were enrolled and four completed the study. All subject records were reviewed to verify that all data in source documents matched data recorded line listings (derived from eCRFs) and that informed consents and assents were appropriately completed. In addition, 1572s, financial disclosure forms, site delegation logs, drug accountability records, IRB approval and dates, and sponsor monitoring records were reviewed. There were no limitations to the inspection.

b. **General observations/commentary:**

The inspection of Dr. Asbell's site revealed regulatory violations. A Form FDA 483, Inspectional Observations, was issued to this investigator for:

- i. Failure to conduct the study according to the signed investigator statement and the investigational plan [21 CFR 312.60]. Specifically, in Study #434 for enrolling 2 or 6 subjects not eligible for the study, permitting clinical assessments to be completed by physicians not listed as sub-investigators on Form FDA 1572s at the time they performed examinations, and for failing to collect and/or appropriately ship microbiologic specimens according to protocol directions.
- ii. Failure to ensure that all changes in research activity were approved by an Institutional Review Board (IRB) prior to implementation [21 CFR 312.66]. Specifically, for failure to obtain IRB approval prior to implementing Amendment 1 and Amendment 2 of the protocol.

c. **Assessment of data integrity:**

Based on the Establishment Inspection Report (EIR) and associated exhibits provided by the FDA investigator, and Dr Asbell's response to Form FDA 483 observations, it appears that Dr. Asbell did not provide adequate oversight to site staff involved in the conduct of Study #434. Lack of oversight of an inexperienced study coordinator (who is no longer employed at the site), in particular, appears to have resulted in numerous errors in performance of study related activities and poor compliance with GCP standards. The numerous deficiencies identified at this site raise concerns regarding the conduct of this study at this site, and question the reliability of efficacy data from this site. Therefore, DSI recommends that efficacy data from this site not be used to support

approval of the NDA. Safety data from this site may be used to support approval of the NDA.

While multiple regulatory violations occurred at the site during the conduct of Study #434, based on the FDA investigator's review of a subsequently conducted study it appears that the site has implemented measures to prevent the reoccurrence of these types of violations. Therefore, DSI has determined the final classification of this inspection to be VAI.

**7. Bausch & Lomb Incorporated**

1400 North Goodman Street  
Rochester, NY 14609

**a. What was inspected:**

This inspection was conducted in accordance with Compliance Program 7348.810 between 09/02/2008-09/05/2008. The inspection was directed to assess the adequacy of sponsor/monitor/CRO functions for clinical trials, #373, #433, and #434. The inspection focused on the selection, monitoring and data validation of clinical investigators, monitoring procedures and activities, adverse event reporting, data collection and handling, test article accountability, and contract responsibilities (CRO, data collection, and laboratory support) related to these studies. A total of nine of the Sponsor's CI files were reviewed in depth. There were no limitations to the inspection.

**b. General observations/commentary:**

The inspection of Bausch & Lomb, Inc. revealed that there were deficiencies in Sponsor/Monitor/CRO oversight of one of nine clinical investigators for whom the Sponsor's files were reviewed (Buhilda McGriff, Study #434). A Form FDA 483, Inspectional Observations, was issued to Bausch & Lomb, Inc. for:

- i. Failure to select only investigator's qualified by training and experience as appropriate experts to investigate the drug [21 CFR 312.53(a)].

Specifically for use of Buhilda McGriff, MD as a CI for Study #434 when supporting documentation to qualify the CI and site staff was inadequate. While the CI stated during the initial qualification monitoring visit that she was experienced in clinical trial conduct, there was no evidence of this experience on her CV and the sponsor did not seek additional evidence to support that the CI had prior clinical trial experience.

**DSI Reviewer Comment: Based on DSI's review of the EIR for the FDA inspection of CI McGriff it appears probable that this CI had limited clinical trial research experience prior to the conduct of this study. From the review of exhibits contained with the McGriff EIR and the**

**NDA data base, however, it appears that the sponsor appropriately addressed the protocol deviations that occurred at the site in analyses (i.e. subjects involved were not included in per protocol analyses).**

**a. Assessment of data integrity:**

While the FDA sponsor inspection revealed a regulatory violation of sponsor obligations in the conduct of Study #434 (selection of an investigator without substantiating their prior research experience in accordance with Bausch & Lomb, Inc Standard Operating Procedures), overall data submitted by the Applicant in the NDA appear reliable, with the exception of data from Dr. Zosa and perhaps Dr. Asbell. In their letter date September 17, 2008, the Sponsor has provided adequate assurance that their method for clinical site selection is being revised and improved.

**IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS**

In general, Protocol #373, Protocol #433 and Protocol #434 appear to have been conducted adequately and the data in support of the NDA appear reliable with the following caveats:

1. For Study #433 at Dr. Kanengiser's site data for portions of biomicroscopy examinations, for the six subjects noted, were incorrectly transcribed from source data into the eCRF. NDA analyses (secondary analyses) utilizing these data points are impacted; although, given the small number of subjects involved the overall impact on analyses is not likely to be significant.
2. Due to serious regulatory violations observed during the CI inspection of Dr. Zosa (Study #433), DSI considers data from this site to be unreliable and recommends that data from this site not be used to support approval of the NDA.
3. Due to the types of regulatory violations observed during the CI inspection of Dr. Asbell (Study #434), DSI considers the efficacy data from this site to be unreliable and recommends that efficacy data from this site not be used to support approval of the NDA; however, the safety data may be used.

*{See appended electronic signature page}*

Jean M. Mulinde, M.D.  
Good Clinical Practice Branch II  
Division of Scientific Investigations

CONCURRENCE:

*{See appended electronic signature page}*

Tejashri Purohit-Sheth, M.D.  
Branch Chief

Good Clinical Practice Branch II  
Division of Scientific Investigations

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/s/

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Jean Mulinde  
5/29/2009 07:21:12 AM  
MEDICAL OFFICER

Tejashri Purohit-Sheth  
5/29/2009 08:11:32 AM  
MEDICAL OFFICER

MEMORANDUM

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

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CLINICAL INSPECTION SUMMARY

DATE: 02-20-2009

TO: Alison Rodgers, Regulatory Project Manager  
Martin Nevitt, M.D., Medical Officer  
Division of Anti-Infective and Ophthalmic Products

FROM: Jean Mulinde, M.D.  
Good Clinical Practice Branch 2  
Division of Scientific Investigations

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

SUBJECT: Evaluation of Clinical Inspections.

NDA: 22-308

APPLICANT: Bausch & Lomb Incorporated

DRUG: Optura™ (besifloxacin hydrochloride ophthalmic suspension, 0.6%  
as base)

NME: Yes

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATIONS: 1. Treatment of bacterial conjunctivitis

CONSULTATION REQUEST DATE: 07/18/2009

DIVISION ACTION GOAL DATE: 04/02/2009

PDUFA DATE: 04/02/2009

## I. BACKGROUND:

Optura™ (besifloxacin hydrochloride ophthalmic suspension, 0.6% as base) is a new molecular entity that belongs to the class of fluoroquinolone anti-infectives. Its mechanism of action involves the inhibition of both bacterial DNA gyrase and topoisomerase IV. Based on *in vitro* microbiologic data, besifloxacin is predicted to have clinical efficacy against aerobic, facultative, and anaerobic Gram-positive and Gram-negative bacteria, including those common pathogens causing bacterial conjunctivitis (e.g., *Staphylococcus aureus*, *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Corynebacter* species, and *Moraxella* species). In NDA 22-308, the Applicant (Bausch & Lomb Inc.) has requested that besifloxacin hydrochloride ophthalmic suspension be approved for the treatment of bacterial conjunctivitis. To support approval, the Applicant has provided data from three pivotal clinical trials (Protocol #373, Protocol #433, and Protocol #434), which they believe provide sufficient evidence for the safety and efficacy of besifloxacin dosed three times daily for 7 days for proposed indication.

The protocols inspected include:

1. Protocol #373: A Study to Evaluate the Clinical and Microbial Efficacy of 0.6% ISV-403 Compared to Vehicle in the Treatment of Bacterial Conjunctivitis

This study was a multicenter, randomized, double-masked, parallel Phase 2 trial conducted at 35 centers in the United States. Patients were to receive either 0.6% ISV-403 (besifloxacin) chloride or ISV-403 vehicle to be instilled to infected eye(s) as one drop at 6-hour intervals (3 times a day) for 5 days. Patients were enrolled in the study from December 28, 2004 through June 7, 2005 (Date of final study report: April 4, 2008).

The primary efficacy endpoints of this study were clinical resolution and eradication of baseline bacterial infection at Visit 3 (study Day 8 +1 day). Clinical resolution was defined as the absence of the following three clinical signs: conjunctival discharge, bulbar conjunctival injection, and palpebral conjunctival injection. All subjects who were randomly assigned to treatment and that had bacteriologically confirmed conjunctivitis were evaluated for the primary endpoints in the intent-to-treat analyses. Key secondary endpoints were:

- individual signs and symptoms
- investigator global ratings
- microbiological and clinical outcome rates on a 0 to 3 scale.

Safety measurements included adverse events, visual acuity changes, biomicroscopy evaluations and ophthalmoscopy.

2. Protocol #433: A Study to Evaluate the Clinical and Microbial Efficacy of 0.6% ISV-403 Compared to Vehicle in the Treatment of Bacterial Conjunctivitis

This study was a multicenter, randomized, double-masked, vehicle-controlled, parallel-group Phase 3 trial conducted at 58 centers in the United States. Patients were to receive besifloxacin Hydrochloride Ophthalmic Suspension, 0.6% as a base (besifloxacin) or vehicle suspension instilled in infected eye(s) as one drop 3 times a day for 5 days. Patients were enrolled in the study from June 5, 2006 through November 7, 2007 (Date of final study report: April 8, 2008).

The primary efficacy endpoints of this study were clinical resolution and eradication of baseline bacterial infection at Visit 2 (study Day 5  $\pm$ 1 day). Clinical resolution was defined as the absence of the following two clinical signs: ocular discharge, and bulbar conjunctival injection. All subjects who were randomly assigned to treatment and that had bacteriologically confirmed conjunctivitis were evaluated for the primary endpoints in the intent-to-treat analyses. Key secondary endpoints were:

- clinical resolution at Day 8, as defined for the primary endpoint
- microbial eradication of baseline infection at Day 8
- individual signs and symptoms at each follow-up visit

Safety measurements included adverse events, visual acuity changes, biomicroscopy evaluations and ophthalmoscopy.

3. Protocol #434: A Study to Evaluate the Clinical and Microbial Efficacy of 0.6% ISV-403 Compared to Vigamox in the Treatment of Bacterial Conjunctivitis

This study was a multicenter, randomized, double-masked, active-controlled, parallel-group Phase 3 trial conducted at 84 centers in the United States and Asia. Patients were to receive either besifloxacin Hydrochloride Ophthalmic Suspension, 0.6% as a base (besifloxacin) or Vigamox (moxifloxacin hydrochloride ophthalmic solution) instilled in infected eye(s) as one drop 3 times a day for 5 days. Patients were enrolled in the study from June 6, 2006 through July 13, 2007 (Date of final study report: March 28, 2008).

The primary efficacy endpoints of this study were clinical resolution and eradication of baseline bacterial infection at Visit 2 (study Day 5  $\pm$ 1 day). Clinical resolution was defined as the absence of the following two clinical signs: ocular discharge, and bulbar conjunctival injection. All subjects who were randomly assigned to treatment and that had bacteriologically confirmed conjunctivitis were evaluated for the primary endpoints in the intent-to-treat analyses. Key secondary endpoints were:

- clinical resolution at Day 8, as defined for the primary endpoint
- microbial eradication of baseline infection at Day 8
- individual signs and symptoms at each follow-up visit

Safety measurements included adverse events, visual acuity changes, biomicroscopy evaluations and ophthalmoscopy.

Four clinical investigators, each of whom contributed large numbers of subjects to the study that they participated in and that were noted to have large numbers of protocol deviations reported in the NDA, were chosen for FDA PDUFA inspections. As the product was a new molecular entity an inspection of the Sponsor was also conducted. In addition, the Final Study Reports contained in NDA 22-308 identified a number of clinical investigators (CI) that had been terminated as CIs from studies early by the sponsor as a result of “continued major GCP non-compliance” and DSI determined that FDA For Cause/PDUFA inspections were indicated at two of these CI sites. The reasons that Bausch & Lomb Incorporated terminated these two sites are summarized below (from General Communication to IND 64, 335, Serial 0060, dated June 5, 2008):

- Protocol #433 Noli R. Zosa, M.D. - Site failed to follow visit window and subject eligibility requirements (e.g. ocular discharge was absent at time of enrollment), investigator demonstrated a general lack of understanding of protocol requirements and awareness of GCP.
- Protocol #434 Penny Asbell, M.D. - Site randomized subjects incorrectly, failed to follow visit window requirements and proper bacterial culture techniques (e.g. cultures shipped under improper conditions); in addition to inadequate investigator supervision of study and informed consent process overall.

## II. RESULTS (by Site):

Name of CI, IRB, or Sponsor Location	Protocol # Site # # of Subjects	Inspection Date	Final Classification
Lee E. Rigel, O.D. VisionCare Associates 310 W. Lake Lansing Rd. Lansing, MI 48823	Protocol #373 Site #033 30 Subjects	09/08/2008- 09/11/2008	VAI
Warren H. Heller, M.D. Arizona Center for Clinical Trials 515 W. Buckeye Rd, #206 Phoenix, AZ 85003	Protocol #433 Site #725416 78 Subjects	09/11/2008- 09/15/2008	NAI
Bruce E. Kanengiser, M.D. Clinical Research Laboratories, Inc. 371 Hoes Lane Piscataway, NJ 08854 USA	Protocol #433 Site #700440 71 Subjects	08/26/2008- 09/24/2008	VAI
Noli R. Zosa, M.D. 8337 Telegraph Road, Suite 125A Pico Rivera, CA 90660	Protocol #433 Site #691449 4 Subjects	10/02/2008- 10/07/2008	Pending (Preliminary classification OAI)
Buhilda McGriff, M.D. Carolina Pediatric Eye Specialists 992 Copperfield Blvd Concord, NC 28025	Protocol #434 Site #750393 52 Subjects	08/28/2008- 09/04/2008	VAI
Penny A. Asbell, M.D.	Protocol #434	Inspection pending	-

100 <sup>th</sup> Street & Madison Ave Annenberg Bldg 22 Floor, Suite22 New York, NY 10029	Site #748395 6 Subjects		
Bausch & Lomb Incorporated 1400 North Goodman Street Rochester, NY 14609	NDA #22-308 Protocol #373 Protocol #433 Protocol #434	09/02/2008- 09/05/2008	VAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary, letter has not yet issued to the CI.

**1. Lee Rigel, OD**

VisionCare Associates  
310 W. Lake Lansing Rd.  
Lansing, MI 48823  
Protocol #373, Site #033

**a. What was inspected:**

This inspection was conducted in accordance with Compliance Program 7348.811 between 09/08/2008-09/11/2008. A total of 30 subjects were screened, 30 subjects were enrolled and 27 completed the study. Three subjects were withdrawn due to insufficient therapeutic response. Records for all 30 subjects were reviewed to verify that eligibility criteria were met, that all data in CRFs matched source documents and line listings, and that informed consents and assents were appropriately completed. In addition, drug accountability records, IRB approval and dates, and sponsor monitoring records were reviewed. There were no limitations to the inspection.

**b. General observations/commentary:**

The inspection of Dr. Rigel's site revealed regulatory violations. A Form FDA 483, Inspectional Observations, was issued to this investigator for failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the inspection. [21 CFR 312.62 (b)] The specific observations included failure to completely document the timing of and personnel administering pregnancy tests and failure to document the method of birth control by several subjects of child-bearing potential.

**c. Assessment of data integrity:**

Although a regulatory violation was noted, it is unlikely that it significantly affects overall reliability of safety and efficacy data from the site. Based on the provided Establishment Inspection Report (EIR) for this site, data derived from Dr. Rigel's site are considered acceptable.

2. **Warren H. Heller, MD**

Arizona Center for Clinical Trials  
515 W. Buckeye Rd, #206  
Phoenix, AZ 85003  
Protocol #433, Site #725416

a. **What was inspected:**

This inspection was conducted in accordance with Compliance Program 7348.811 between 09/11/2008-09/15/2008. A total of 79 subjects were screened, 78 subjects were enrolled and 69 completed the study. Records for 20 subjects were reviewed to verify that eligibility criteria were met, that all data in CRFs matched source documents and line listings, and that informed consents and assents, if indicated, were appropriately completed. In addition, drug accountability records, IRB approval and dates, and sponsor monitoring records were reviewed. There were no limitations to the inspection.

b. **General observations/commentary:**

The inspection of Dr. Heller's site did not reveal regulatory violations. A Form FDA 483, Inspectional Observations, was not issued.

c. **Assessment of data integrity:**

Based on the provided Establishment Inspection Report (EIR) for this site, data derived from Dr. Heller's site are considered acceptable.

3. **Bruce E. Kanengiser, MD**

Clinical Research Laboratories, Inc.  
371 Hoes Lane  
Piscataway, NJ 08854 USA  
Protocol #433, Site #700440

a. **What was inspected:**

This inspection was conducted in accordance with Compliance Program 7348.811 between 08/26/2008-09/24/2008. A total of 73 subjects were screened, 71 subjects were enrolled and 69 completed the study. During the inspection, 100% of the data were audited, (comparing the source record, eCRF, and data listings provided in the NDA) for subject eligibility criteria, clinical assessment and global change ratings, visual acuity results, direct ophthalmoscopy results, microbiologic results, concomitant medication use, study drug dispensing, adverse events, subject discontinuations, and protocol violations. Fifty percent of subject data were audited for biomicroscopy results. In addition, informed consent documents, drug accountability records, IRB approval and dates, and sponsor monitoring records were reviewed. There were no limitations to the inspection.

b. **General observations/commentary:**

The inspection of Dr. Kanengiser's site revealed regulatory violations. A Form FDA 483, Inspectional Observations, was issued to this investigator for:

- i. Failure to obtain informed consent in accordance with 21 CFR Part 50 from each human subject prior to drug administration. Specifically, for failing to obtain assent from four subjects (Subjects #0398, #0399, #0696, and #0800) between the ages to 6 and 11 years and failing to obtain consent from one subject (Subject #0523) between the age of 12 and 18 years as was required by the protocol and/or study plan.

**DSI Reviewer Comment:** DSI notes, however, that in each case informed consent documents were signed by the subjects' legally authorized representatives.

- ii. Failure to ensure that all changes in research activity were approved by an Institutional Review Board (IRB) prior to implementation [21 CFR 312.66]. Specifically, for failing to obtain approval from the IRB prior to increasing enrollment numbers at the site and for failing to notify the IRB of actual enrollment of children in the study in 3 progress reports made to the IRB. While the protocol and consents originally approved by the IRB allowed enrollment of pediatric subjects, the site failed to accurately complete the section of required q6mo study status reports submitted that would inform them of the status of pediatric subject enrollment at the site.
- iii. Failure to provide updated financial information to the study sponsor when relevant changes occurred during the course of the investigation [21 CFR 312.64(d)]. Specifically, for failing to provide the sponsor with financial disclosure forms completed and signed by two foreign medical doctors who made a direct and significant contribution to the study data.

**DSI Reviewer Comment:** Based on DSI's review of the CI's response dated September 29, 2008, the CI has obtained and forwarded to the sponsor a completed financial disclosure form from one of these individuals. The second individual is no longer in his employ, but he has provided evidence that he has attempted to secure a completed financial disclosure form from this individual as well, though without success.

- iv. Failure to prepare or maintain accurate case histories with respect to observations and data pertinent to the investigation [21 CFR 312.62(b)]. Specifically, for incorrectly recording in the eCRF portions of Visit 1 biomicroscopy examinations (chemosis and/or hyperemia results) for six of thirty-six subjects (Subjects #0247, #0263, #0528, #0621, #0265, and #0619) audited. In each case source documents described the condition as 2=Mod or 1=Mild and the value recorded in the eCRF was 0=None.

Subject #	Visit	Eye	Condition	Degree (Source Document)	Degree (eCRF)
0247	1	OD	Chemosis	2=Mod	0=None
0247	1	OS	Chemosis	1=Mild	0=None
0263	1	OS	Hyperemia	1=Mild	0=None
0528	1	OD	Hyperemia	1=Mild	0=None
0528	1	OS	Hyperemia	1=Mild	0=None
0621	1	OD	Hyperemia	1=Mild	0=None
0621	1	OS	Hyperemia	1=Mild	0=None
0265	1	OD	Chemosis	1=Mild	0=None
0265	1	OS	Chemosis	1=Mild	0=None
0619	1	OS	Hyperemia	1=Mild	0=None
0619	1	OS	Chemosis	1=Mild	0=None

v. Failure to ensure that the investigation was conducted according to the signed investigator statement and the investigational plan [21 CFR 312.60]. Specifically for:

- a) Failing to list two sub-investigators on Form FDA 1572s submitted to the sponsor.
- b) Failing to adequately document that the CI was not present during instillation of in-office study medication drops during Visit 1 and/or Visit 2 study procedures. Statements were made in source documents for each subject that the CI was not present, but these statements were not signed, initialed, or dated by the individual making them in many cases.
- c) Storage conditions for study drug, as required by the protocol, were not documented for four of 33 weeks reviewed during the audit and storage temperatures fell outside of the protocol required storage at 59-77°F for a portion of 19 of 33 weeks audited. The upper bound temperature could not be ascertained because the needle used by the device appears to have run off the paper recording discs (highest temp on disc = 120°F).

**DSI Reviewer Comment:** Based on DSI's review of the EIR it seems unlikely that room temperature conditions would have reached temperatures as high as 120°F during the time periods recorded (October through April in New Jersey); therefore, DSI considers it likely that the findings are secondary to device malfunction. In the CI's response dated September 29, 2008, he has provided evidence that this device has subsequently been replaced to prevent further such occurrences in future studies.

- d) Failure to attempt to contact one subject that did not present for a required visit as was required in Section 8.5.4 of the protocol.

- vi. Failure to return unused supplies of an investigational drug to the sponsor [21 CFR 312.62(a)]. Specifically, the protocol required that all used and unused units of investigational material be returned to the sponsor, but documentation that the site was inadequate to assure that all used and unused units were returned Bausch & Lomb.

**DSI Reviewer Comment: Based on DSI's review of the CI's response dated September 29, 2008, study monitors did document in monitoring reports that used and unused units were returned to the sponsor, but documentation was not specific as to kit numbers/vial numbers returned. While it appears likely that study drug was appropriately disposed of during and at the conclusion of the study, DSI considers site's lack of adequately detailed disposition records to be regulatory violation.**

- c. **Assessment of data integrity:**  
While multiple regulatory violations occurred at this site it does not appear that subject safety was compromised. Overall efficacy and safety data appear reliable with the exception of the data noted for the six subjects described in section iv.
4. **Noli R. Zosa, MD**  
8337 Telegraph Road, Suite 125A  
Pico Rivera, CA 90660  
Protocol #433, Site #691449

a. **What was inspected:**

This inspection was conducted in accordance with Compliance Program 7348.811 between 10/02/2008-10/07/2008. A total of four subjects were screened, four subjects were enrolled and one appears to have completed the study. Two subjects were withdrawn from the study when study monitors determined that they did not meet eligibility criteria. Based on study documents available at the site, it could not be determined if the fourth subject completed the study. Available records for all subjects were reviewed. Records were limited to printed eCRF documents for 3 subjects and no source documentation was available to substantiate these subjects' existence and eligibility to participate in the study. For one subject both the eCRF and a patient chart were available, but there was no documentation of the subject's participation in the study in the patient's chart. A regulatory binder was available for review at the site that contained the following items for review: communications between the site and the IRB, a delegation of authority of clinical responsibilities for the study, CI Form FDA 1572s, a monitoring visit log, a test article accountability log, and communications from study monitors to the CI. The absence of study related source documents specific to enrolled subjects was a limiting factor for this inspection.

**b. General observations/commentary:**

The inspection of Dr. Zosa's site revealed regulatory violations. A Form FDA 483, Inspectional Observations, was issued to this investigator for:

- i. Failure to conduct the study according to the signed investigator statement and the investigational plan [21 CFR 312.60]. Specifically, for:

Three of four enrolled subjects did not meet study eligibility criteria. Subject #1054 and Subject #0155 did not have minimum scores required for ocular discharge and Subject #0156 was less than one year old.

- ii. Failure to obtain informed consent in accordance with 21 CFR Part 50 from each human subject prior to drug administration. Specifically for:

Signed informed consent documents were not present for any of the four subjects enrolled by the CI.

- iii. Failure to prepare or maintain adequate case histories with respect to observations and data pertinent to the investigation [21 CFR 312.62(b)]. Specifically for:

There were no source documents in the CI's records to corroborate entries made on the electronic case report forms for the clinical study for Study #433. Source documents not on file included: ophthalmologic assessments, visual acuity assessments, laboratory requisitions, subject medical charts, laboratory reports for collected specimens, subject diaries documenting daily drug administration, and documentation of pregnancy testing (when indicated).

**c. Assessment of data integrity:**

There are multiple items listed on the Form FDA 483 and detailed in the EIR for this CI that raise serious concerns with data reliability and integrity at this site; therefore, DSI recommends that data from this site not be used to support approval of the NDA.

**5. Buhilda McGriff, MD**

Carolina Pediatric Eye Specialists  
992 Copperfield Blvd  
Concord, NC 28025  
Protocol #434, Site #750393

**a. What was inspected:**

This inspection was conducted in accordance with Compliance Program 7348.811 between 09/08/2008-09/11/2008. A total of 58 subjects were screened, 52 subjects were enrolled and 48 completed the study. Records for 22 subjects were reviewed to verify that data recorded in NDA line listings and subjects' case report forms were the same as information documented in source records. A random review for adverse events revealed that all adverse events appear to have been appropriately reported. In addition, drug accountability records, IRB approval and dates, and sponsor monitoring records were reviewed. There were no limitations to the inspection.

**b. General observations/commentary:**

The inspection of Dr. McGriff's site revealed regulatory violations. A Form FDA 483, Inspectional Observations, was issued to this investigator for:

- i. Failure to obtain informed consent in accordance with 21 CFR Part 50 from each human subject prior to drug administration. Specifically for:
  - a) Conduct of study related procedures and dosing of two subjects (Subject #0406 and Subject #0407) occurred prior to their signing the study informed consent document.
  - b) Written informed consent not being properly documented in that written informed consent was not appropriately completed by either the subject or their legally authorized representative and/or by the individual conducting the informed consent discussion for five subjects. Observations included signing of informed consent by individual conducting the informed consent discussion at a date after the informed consent was signed by subjects in four cases (Subject #0045, Subject #0406, Subject #0407, and Subject #1015) and that subjects signed some, but not all places required in the informed consent document (Subject #0045, Subject #0406, and Subject #1014).
  - c) Study Assent Forms were to have been signed only by subjects between the ages of 6 to 11 years. Assent Forms were also signed, by the subject or by their legally authorized representative, for at least 15 subjects that were less than 6 years of age or greater than 11 years of age.
- iv. Failure to conduct the study according to the signed investigator statement and the investigational plan [21 CFR 312.60]. Specifically, for:
  - a) Failure to conduct study visits between the hours of 7am and 10am for two subjects as specified by the protocol (Subject #0045 Visit 3 and Subject #0407 Visit 2).
  - b) Subjects were not to self administer study drug on the morning of study visit 2. This dose was to be administered at the CI site after the visit 2 assessment and eye culture. Five subjects, however, administered a dose of study drug in the AM prior to visit 2 (Subjects #0406, #0407, #0828, #1152, and #1231).

c) The protocol stated that study medication was to be instilled in the infected eye three times a day for Day 1 to Day 5 of the study. Four subjects did not administer doses according to this regimen. Subject #0406 and Subject #0407 continued to use study medication Days 6, 7, and 8. Subject #1085 and Subject #1086 missed two doses on Day 5 and continued to use study medication on Days 6, 7, and 8.

c. **Assessment of data integrity:**

Although regulatory violations were noted in i) a) above, it is unlikely that they significantly affect overall reliability of safety and efficacy data from the site. Observations included in i) b) are not considered valid regulatory violations as the FDA does not have the regulatory authority to require signature of HIPPA related documents or to require that informed consent documents be witnessed (other than as specified for emergency use). Item i) c), while factual, does not impact the reliability of data submitted by this site. Regarding the protocol deviations noted for subjects in ii) above, it appears that the Sponsor appropriately excluded these subjects from the per protocol analyses in the NDA submission. The data is considered acceptable from this site.

6. **Penny A. Asbell, MD**  
100th Street & Madison Ave  
Annennberg Bldg 22 Floor, Suite22  
New York, NY-10029  
Protocol #434, Site #748395

**This inspection has not been completed and the report is not available from the field. Based on review of information contained in the FDA investigator's establishment inspection report (EIR) for the sponsor inspection, it is likely that significant regulatory violations (informed consent errors, drug accountability issues, randomization errors, failure to follow the investigational plan) occurred at this site. During the FDA inspection of Bausch & Lomb, the sponsor stated that data from the six subjects enrolled at this site had not been used in efficacy analyses, but that data from these subjects was utilized in safety analyses supporting the NDA. An inspection summary addendum will be generated after the inspection has been completed and the results have been evaluated by DSI.**

7. **Bausch & Lomb Incorporated**  
1400 North Goodman Street  
Rochester, NY 14609

a. **What was inspected:**

This inspection was conducted in accordance with Compliance Program 7348.810 between 09/02/2008-09/05/2008. The inspection was directed to assess the adequacy of sponsor/monitor/CRO functions for clinical trials, #373, #433, and #434. The inspection focused on the selection, monitoring and data validation of clinical investigators, monitoring procedures and activities, adverse event reporting, data collection and handling, test article accountability, and contract responsibilities (CRO, data collection, and laboratory support) related to these studies. A total of nine of the Sponsor's CI files were reviewed in depth. There were no limitations to the inspection.

b. **General observations/commentary:**

The inspection of Bausch & Lomb, Inc. revealed that there were deficiencies in Sponsor/Monitor/CRO oversight of one of nine clinical investigators for whom the Sponsor's files were reviewed (Buhilda McGriff, Study #434). A Form FDA 483, Inspectional Observations, was issued to Bausch & Lomb, Inc. for:

- i. Failure to select only investigator's qualified by training and experience as appropriate experts to investigate the drug [21 CFR 312.53(a)].

Specifically for use of Buhilda McGriff, MD as a CI for Study #434 when supporting documentation to qualify the CI and site staff was inadequate. While the CI stated during the initial qualification monitoring visit that she was experienced in clinical trial conduct, there was no evidence of this experience on her CV and the sponsor did not seek additional evidence to support that the CI had prior clinical trial experience.

**DSI Reviewer Comment:** Based on DSI's review of the EIR for the FDA inspection of CI McGriff it appears probable that this CI had limited clinical trial research experience prior to the conduct of this study. From the review of exhibits contained with the McGriff EIR and the NDA data base, however, it appears that the sponsor appropriately addressed the protocol deviations that occurred at the site in analyses (i.e. subjects involved were not included in per protocol analyses).

a. **Assessment of data integrity:**

While the FDA sponsor inspection revealed a regulatory violation of sponsor obligations in the conduct of Study #434 (selection of an investigator without substantiating their prior research experience in accordance with Bausch & Lomb, Inc Standard Operating Procedures), overall data submitted by the Applicant in the NDA appear reliable, with the exception of data from Dr. Zosa and perhaps Dr. Asbell. In their letter date September 17, 2008, the Sponsor has provided adequate assurance that their method for clinical site selection is being revised and improved.

**IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS**

In general, Protocol #373, Protocol #433 and Protocol #434 appear to have been conducted adequately and the data in support of the NDA appear reliable with the following caveats:

1. For Study #433 at Dr. Kanengiser's site data for portions of biomicroscopy examinations, for the six subjects noted, were incorrectly transcribed from source data into the eCRF. NDA analyses (secondary analyses) utilizing these data points are impacted; although, given the small number of subjects involved the overall impact on analyses is not likely to be significant.
2. Due to serious regulatory violations observed during the CI inspection of Dr. Zosa (Study #433), DSI considers data from this site to be unreliable and recommends that data from this site not be used to support approval of the NDA.
3. The For Cause inspection of Dr. Asbell has not been completed and a report is not available from the field. Based on the review of monitoring reports from this site, which were reviewed during the sponsor inspection, it is likely that significant regulatory violations occurred at this site. DSI notes that during the sponsor inspection, the sponsor stated that efficacy data from this site had been excluded in NDA analyses.

Note that a CIS addendum to describe the findings pertinent to Dr. Asbell will be submitted upon receipt and review of the EIR and supporting documents.

*{See appended electronic signature page}*

Jean M. Mulinde, M.D.  
Good Clinical Practice Branch II  
Division of Scientific Investigations

CONCURRENCE:

*{See appended electronic signature page}*

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

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/s/

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Jean Mulinde  
2/23/2009 03:19:33 PM  
MEDICAL OFFICER

Tejashri Purohit-Sheth  
2/23/2009 03:31:34 PM  
MEDICAL OFFICER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration  
Rockville, MD 20857

NDA 22-308

**PROPRIETARY NAME REQUEST  
- CONDITIONALLY ACCEPTABLE**

Bausch and Lomb, Inc.  
ATTENTION: Jennifer S. Knicley, Manager, Regulatory Affairs  
1400 North Goodman Street  
Rochester, New York 14609

Dear Ms. Knicley:

Please refer to your New Drug Application (NDA) dated May 30, 2008, received June 2, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Besifloxacin Ophthalmic Suspension, 0.6%.

We also refer to your January 8, 2009, correspondence, received January 9, 2009, requesting review of your proposed proprietary name, Besivance. We have completed our review of the proposed proprietary name, Besivance and have concluded that it is acceptable.

The proposed proprietary name, Besivance, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If any of the proposed product characteristics as stated in your January 8, 2009, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Marlene Hammer, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 301-796-0757. For any other information regarding this application, contact Alison Rodgers, Project Manager in the Division of Anti-Infective and Ophthalmology Products.

Sincerely,

*{See appended electronic signature page}*

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

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Wiley Chambers  
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**MEMORANDUM**

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

**DATE:** March 9, 2009

**TO:** File

**FROM:** Alison Rodgers

**SUBJECT:** **Pre-Approval Safety Conference**  
NDA 22-308, Besivance (besifloxacin hydrochloride ophthalmic suspension , 0.6%) Drops

The Pre-Approval Safety Conference for Besivance took place on March 2, 2009. Attendees included: Ed Cox, Wiley Chambers, Martin Nevitt, Chuck Bonapace, Ryan Owen, Fred Marsik, John Metcalfe, and Darrell Jenkins.

The Division reported that no safety issues to be followed after approval had been identified.

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/s/

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Alison Rodgers  
3/9/2009 12:59:19 PM  
CSO

Alison Rodgers  
3/9/2009 12:59:50 PM  
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

**FILING COMMUNICATION**

NDA 22-308

Bausch & Lomb Incorporated  
Attention: Jennifer S. Knicley  
Manager, Regulatory Affairs  
1400 North Goodman Street,  
Rochester, NY 14609

Dear Ms. Knicley:

Please refer to your new drug application (NDA) dated May 30, 2008, received June 2, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Besifloxacin Hydrochloride Ophthalmic Suspension, 0.6% as base.

We also refer to your submission dated December 21, 2007.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is 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 April 2, 2009.

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 age one (1) to eighteen (18). 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 Alison Rodgers, Regulatory Project Manager, at (301) 796-0797.

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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Wiley Chambers  
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 22-308

**NDA ACKNOWLEDGMENT**

Bausch & Lomb Incorporated  
Attention: Jennifer S. Knicley  
Manager, Regulatory Affairs  
1400 North Goodman Street  
Rochester, NY 14609

Dear Ms. Knicley:

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

Name of Drug Product: Besifloxacin Hydrochloride Ophthalmic Suspension, 0.6% as base

Date of Application: May 30, 2008

Date of Receipt: June 2, 2008

Our Reference Number: NDA 22-308

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 August 1, 2008, 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/dataacouncil/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 conform to the content and format requirements of revised 21 CFR 201.56-57.

The NDA number provided above should 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

NDA 22-308

Page 2

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 Alison Rodgers, Regulatory Project Manager, at (301) 796-0797.

Sincerely,

*{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/

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Maureen Dillon-Parker  
6/27/2008 12:02:02 PM  
NDA 22-308 Ack Ltr



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 64,335

Bausch & Lomb, Inc.  
Attention: Jennifer S. Knicley  
Manager, Regulatory Affairs  
1400 North Goodman Street  
Rochester, NY 14609-3547

Dear Ms. Knicley:

Please refer to your Investigational New Drug Application (IND) file for ISV-403 ophthalmic suspension.

We also refer to the meeting between representatives of your firm and the FDA on June 6, 2007. The purpose of the meeting was to discuss submission of a new drug application for this product.

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 Alison Rodgers, Regulatory Project Manager, at (301) 796-0797.

Sincerely,

*{See appended electronic signature page}*

Edward M. Cox, MD, MPH  
Director  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

Enclosure

**MEMORANDUM OF MEETING MINUTES**

**MEETING DATE:** June 6, 2007  
**TIME:** 3:00 PM  
**LOCATION:** 10903 New Hampshire Avenue, Room 1415, Silver Spring, MD  
**APPLICATION:** IND 64,335  
**DRUG NAME:** ISV-403  
**TYPE OF MEETING:** Pre-NDA

**MEETING CHAIR:** Edward Cox, M.D., MPH

**MEETING RECORDER:** Alison Rodgers

**FDA ATTENDEES:**

**Office of Antimicrobial Products (OAP)**

Edward Cox, MD, MPH, Director (Acting)  
Dave Roeder, Associate Director for Regulatory Affairs

**Division of Anti-Infective and Ophthalmology Products (DAIOP)**

William Boyd, MD, Clinical Team Leader  
Wiley Chambers, MD, Deputy Director  
Amy Ellis, PhD, Pharmacologist  
Jennifer Harris, MD, Medical Officer  
Lucious Lim, MD, Medical Officer  
Rhea Lloyd, MD, Medical Officer  
Fred Marsik, PhD, Microbiology Team Leader  
Martin Nevitt, MD, Medical Officer  
Lin Qi, PhD, Chemist, Office of New Drug Quality Assessment  
Sarah Robertson, PharmD  
Alison Rodgers, Project Manager  
Harold V. Silver, Microbiologist  
Janice Soreth, MD, Director  
Thamban Valappil, PhD, Statistical Team Leader  
Sonal Wadhwa, MD, Medical Officer  
Yan Wang, PhD, Statistician

**EXTERNAL CONSTITUENT ATTENDEES:**

**Bausch & Lomb, Inc.**

Lynne Brunner, Senior Microbiologist  
Timothy Comstock, OD, Director, Pharmaceutical Clinical Science  
Linda Galbier, Manager, CMC Development  
Don Handley, Director, Regulatory Affairs  
Matthew Jonasse, Project Director  
Jennifer Knicley, Manager, Regulatory Affairs  
Michael Paterno, OD, Manager, Pharmaceutical Clinical Science  
Joel Proksch, PhD, Director, Drug Metabolism  
Mary Richardson, PhD, Manager, Global Nonclinical Safety

Dale Usner, PhD, Director, Global Statistical Programs  
John Weet, PhD, Vice President, Global Regulatory Affairs

**BACKGROUND:** Bausch & Lomb, Inc. (Bausch & Lomb) submitted a request for a Pre-NDA meeting on April 5, 2007. The purpose of the meeting is to discuss the adequacy of their current data for ISV-403 and plans for the NDA submission. The Division provided responses to the questions outlined in the briefing package via facsimile on June 4, 2007.

**MEETING OBJECTIVE:**

The objective of the meeting was to clarify the division's responses to the questions outlined in the briefing package for ISV-403 ophthalmic suspension.

**DISCUSSION:**

In response to questions in the May 8, 2007, briefing package, the following responses were provided. The format provides the firm's questions in plain lettering followed by FDA responses in italics. Questions, responses, and additional comments from the meeting are indicated with headings. If there are no additional meeting comments, this is noted and bolded.

**Clinical**

1. Does FDA have any comment on the organization of the Clinical sections within the comprehensive NDA table of contents?

**Reviewer's comments:**

*Outline appears acceptable. Case report forms for all discontinued patients should be included regardless of the reason they were discontinued.*

***No Additional Meeting Comments***

2. We are planning to provide integrated efficacy and safety summaries over the two pivotal Phase 3 studies and single Phase 2 study. For efficacy this will include integrating our end of treatment visit which was Day 4 ± 1 day for the Phase 2 study and Day 5 ± 1 day for the Phase 3 studies. Does FDA concur we can integrate efficacy data across the Phase 2 and Phase 3 studies in this manner?

**Reviewer's comments:**

*The results for efficacy and safety should be provided for each trial separately.*

*An additional analysis for efficacy may combine the end of treatment visit day 4 ± 1 day for the Phase 2 study with the end of treatment visit day 5 ± 1 day for the Phase 3 studies in an integrated efficacy analysis.*

***No Additional Meeting Comments***

3. We are not planning on providing integrated information for efficacy outcomes on all enrolled study eyes; particularly we will not be including in the integrated summaries

subjects when neither eye had a culture indicating baseline pathogenic bacteria levels. Is this acceptable?

**Reviewer's comments:**

*No. Integrated efficacy outcomes should be provided for all enrolled study eyes (the integrated efficacy outcome would include eyes that had bacterial cultures that were positive or negative).*

***No Additional Meeting Comments***

4. As outlined in the Phase 3 protocols, a single eye from each subject will be defined as the study eye. Criteria i and ii below are taken from the Phase 3 protocols for defining the study eye. Criteria iii below has been added here to expand the definition of study eye for the ITT population.
  - i. For subjects with one treated eye having baseline cultures indicating pathogenic bacteria levels and a minimum score of 1 for each of conjunctival discharge and bulbar conjunctival injection at baseline, the study eye will be defined as the treated eye with baseline cultures indicating pathogenic bacteria levels and a minimum score of 1 for each of conjunctival discharge and bulbar conjunctival injection at baseline.
  - ii. For subjects with both treated eyes having baseline cultures indicating pathogenic bacteria levels and a minimum score of 1 for each of conjunctival discharge and bulbar conjunctival injection at baseline, the study eye will be defined as the treated eye with the highest combined sum of the ratings for conjunctival discharge and bulbar conjunctival injection at baseline. If the score is the same for both eyes, the right eye will be considered the study eye.
  - iii. For subjects whose treated eye(s) did not have baseline cultures indicating pathogenic bacteria levels, the study eye will be defined as the eye with a minimum score of 1 for each of conjunctival discharge and bulbar conjunctival injection at baseline and the highest combined sum of the ratings for conjunctival discharge and bulbar conjunctival injection at baseline. If the score is the same for both eyes, the right eye will be considered the study eye.

**Reviewer's comments:**

*For the ITT population, the additional criteria defining the study eye for those treated eyes that did not have baseline cultures indicating pathogenic bacteria levels is acceptable.*

***No Additional Meeting Comments***

- a. The primary analyses of the primary endpoints: proportion of study eyes with clinical resolution and the proportion of study eyes with bacterial eradication will incorporate Cochran-Mantel-Haenszel chi-squared statistics adjusting for site. The primary analysis will use only those study eyes defined in i and ii above (i.e. those eyes that have baseline cultures indicating pathogenic bacteria levels at baseline) and use only observed data, except for subjects who withdraw due to lack of efficacy on or before Visit 2 (Day 5) without clinical or bacterial evaluations at Visit 2. These subjects will be treated as failures in the primary analysis of clinical resolution and microbial eradication for whichever measures they are missing. A secondary analysis of the primary endpoints will incorporate Cochran-Mantel-Haenszel chi-squared statistics

adjusting for site and use all study eyes. If a study eye is missing Day 5 data, the last available on-treatment clinical and bacteriological data will be carried forward. Are these approaches for the primary and secondary analyses acceptable?

**Reviewer's comments:**

*a. It is unclear how you will know that the patient exited due to lack of efficacy, if all patients who do not return for Visit 2 are considered to have exited due to lack of efficacy, the plan is acceptable for Study 433, the superiority trial.*

*For Study 434, the Non-inferiority trial, it is also recommended that patients who do not return for Visit 2 be considered failure, but there are additional issues that you should consider as discussed below.*

*The Center for Drug Evaluation and Research has had a number of internal discussions concerning non-inferiority trials. Although the Ophthalmology Group continues to support the decision made by the Ophthalmic sub-committee of the Advisory Committee that a New Drug Application could be supported by one vehicle controlled study in combination with a non-inferiority study using an active control, that decision is not uniformly supported by other decision making groups within the Center for products which are new molecular entities.*

*The Agency does not have sufficient information to establish the therapeutic effect of Vigamox compared to no treatment, we only have information comparing Vigamox to its vehicle. Estimates of the therapeutic effect compared to vehicle range from 15% using the point estimates, to 3% using the lower confidence limits. Commonly, there is an attempt to retain at least half of the therapeutic effect within the non-inferiority confidence interval. As currently designed, your non-inferiority trial is not designed to retain much, if any, of the therapeutic effect compared to vehicle. We are therefore informing you at this time, that your non-inferiority trial comparing your product to Vigamox is unlikely to be supportive of a new drug application unless your product is statistically superior to Vigamox in the clinical cure rate.*

*In addition, we recommend that the primary analyses be performed using both MITT and per protocol (PP) as co-primary populations and that sensitivity analyses be performed of the proportions of study eyes with clinical resolution and bacterial eradication analyzed using chi-squared statistics without adjusting for study site.*

**Meeting Comments:**

- Regarding Question #4a, Bausch & Lomb stated they would revise the protocol so that any no show or missing data for the primary outcome(s) on visit 2 would be considered as failures in the primary analysis
- Bausch & Lomb stated their concerns regarding the Agency's response to Question #4a regarding non-inferiority trials. They noted that based on guidance from the Division to be consistent with other approved fluoroquinolones, they had chosen Vigamox as the active comparator because it is the leading standard of care. In addition, at the end-of-phase 2 meeting, the Division agreed that the proposed phase 3 studies were acceptable. Bausch & Lomb stated that based on

the approval of Azasite, their data appears to be acceptable. Finally, they noted that ophthalmic products have a different risk/benefit profile so that non-inferiority safety concerns are not an issue with these products.

OAP explained its concerns with Bausch & Lomb's non-inferiority trial comparing ISV-403 to Vigamox noting that the understanding of non-inferiority studies continues to evolve. Generally, two adequate and well controlled trials are needed. OAP stated that in this case two adequate and well controlled trials are required for approval; if one trial is a non-inferiority design, then the Agency needs to know the inferiority margin that will preserve some of the effect due to placebo. OAP also noted that safety and efficacy data would be needed in the pre-approval stage and not as a postmarketing commitment. Regarding Azasite, OAP explained that systemic information is available on azithromycin while it is not for ISV-403. OAP also referenced the ICH E10 guidelines and the weight of evidence needed to study a different formulation and route.

- Bausch & Lomb stated that their phase 2 data was statistically significant and asked if it could be used to support an NDA. OAP responded that the phase 2 data would need to be reviewed to determine what role it could play in supporting an NDA.
  - With the caveat that systemic moxifloxacin data might not necessarily support the ISV-403 application, OAP agreed that Bausch & Lomb could prepare an alternate proposal for the Division to review in the event that the phase 2 data is not acceptable.
- b. As defined above, the primary and secondary analyses will utilize information from only one eye per subject. Additional analyses will provide similar information for treated non-study eyes. Is this acceptable?

**Reviewer's comments:**

*b. Acceptable.*

***No Additional Meeting Comments***

- c. For analysis of microbiological outcome by baseline pathogen, the study eye defined above in i and ii will be used if the study eye's baseline culture indicates the specified baseline pathogen. Otherwise the non-study eye from ii above will be used if the non-study eye indicates the specified baseline pathogen.
- i. Is this acceptable?
  - ii. If both eyes indicate the specified baseline pathogen may we use both eyes in the summary of eradication by baseline pathogen with each eye counted separately as eradicated or not depending on the outcome for that eye?

**Reviewer's comments:**

*c. i. Acceptable.*

*ii No. Only one eye should be designated as the study eye.*

***No Additional Meeting Comments***

5. For the primary analysis of microbiological eradication at the eye level, we define microbiological eradication as all baseline organisms below threshold and no new organism above threshold. Is it acceptable to change this definition to all baseline organisms below threshold?

**Reviewer's comments:**

*No. Eradication should be no organisms.*

***No Additional Meeting Comments***

6. The analysis populations in the Phase 3 protocols are defined as follows:
  - i) Intent to treat (ITT) population includes all randomized subjects, regardless of confirmed bacterial conjunctivitis. Missing Visit 2 (Day 5) data will be imputed using last observation carried forward.
  - ii) Modified ITT (mITT) includes all randomized subjects who received at least one drop of study medication and who have baseline cultures indicating pathogenic bacteria levels. Only observed data will be used, with the exception of subjects who withdraw due to lack of efficacy (as detailed in Question 4.a above).
  - iii) Per protocol (PP) includes subjects in the mITT population who do not have a major protocol violation.
  - iv) Safety includes all subjects who received at least one drop of study medication.

The efficacy analysis for the ITT population will be limited to the primary endpoints of clinical resolution and microbial eradication. This population will not be used in analysis of secondary endpoints (i.e. only mITT and PP will be used for secondary endpoints). Is this acceptable?

**Reviewer's comments:**

*ITT population should also be used in the analysis of secondary endpoints since its comparison with the PP population will establish the robustness of the findings. In addition, please see the response to question 4a.*

**No Additional Meeting Comments**

7. The analysis of ocular adverse events will consist of a table for study eye adverse events as well as a table capturing adverse events that occurred in any treated eye of a subject. The rationale behind the study eye adverse events table is to obtain a level comparison of the frequency of ocular adverse events, in case there is a difference in the average number of treated eyes between the treatments. Is this acceptable?

**Reviewer's comments:**

*It is acceptable to include a table of the analysis of ocular adverse events for study eye adverse events and a table for adverse events occurring in any treated eye. In addition, include a combined (ocular adverse events for study eye + ocular adverse events occurring in any treated eye) table of ocular adverse events.*

**Meeting Comments:**

- The Division agreed that if a subject has both eyes treated and adverse events occur in both eyes, these should be counted as two.
8. Included in the Clinical summary is a list of tables to be included in section 14 of the Phase 3 clinical study reports.
- a. Are there any additional tables that FDA would expect to see?
  - b. Does FDA have any comments in regards to format or other expectations for the tables listed?

**Reviewer's comments:**

- a. *The listing of tables appears adequate. If not currently proposed within the Study Enrollment section, provide a table of subjects enrolled by investigator site and also a table of subjects with clinical cures enrolled by investigator site.*
- b. *There are no additional comments.*

*No Additional Meeting Comments*

**Nonclinical**

9. Based upon the tabulation of studies and table of contents for the Nonclinical reviewable unit, does FDA have any additional recommendations for the presentation of data in the NDA?

**Reviewer's comments:**

*It would be helpful for the Table of Contents to include the title of each study along with the volume and page number where the report can be found in the submission. The Table of Contents in the electronic submission should contain links from the study titles to the study reports.*

*No Additional Meeting Comments*

10. Does the FDA agree with the proposal to presubmit the Nonclinical reviewable unit?

**Reviewer's comments:**

*We have no objection to the proposed presubmission.*

*No Additional Meeting Comments*

**Microbiology**

11. As agreed at the November 17, 2006 meeting with FDA, Bausch & Lomb will use the systemic breakpoint for gemifloxacin to develop the *in vitro* second list in the package insert for ISV-403. Does the agency agree [redacted] is the value Bausch & Lomb should use to compare MIC90 values of non-fastidious and fastidious isolates recovered from 2003-2007 for inclusion in the *in vitro* second list?

b(4)

**Clinical Microbiology Response:**

*No. We are willing to consider an alternative approach in which the MIC<sub>90</sub> is used together with the lowest systemic level (MIC [redacted] is achieved by the approved*

b(4)

*fluoroquinolone product gemifloxacin (assuming that ISV-403 is believed to have pharmacokinetic properties similar to the currently approved fluoroquinolone products).*

**Meeting Comments:**

- Bausch & Lomb stated that they thought they were being consistent with gemifloxacin and other approved ophthalmic fluoroquinolones because [REDACTED] b(4)  
µg/mL is the break point used.
- The Division mentioned that at the last meeting the Sponsor was told that gemifloxacin is the fluoroquinolone requested for comparison to their drug. That the lowest MIC (the more conservative MIC) be used. The lowest MIC [REDACTED] is used for *Streptococcus pneumoniae* and another fastidious microorganism. Also mentioned, is that the Sponsor's suggested MIC [REDACTED] (the less conservative MIC) is used only for *Enterobacteriaceae*. The Division "highly suggested" that the MIC [REDACTED] be used. b(4)

12. Existing *in vitro* and clinical microbiology susceptibility data indicate that SS734 retains bactericidal activity against a variety of ocular pathogens which are resistant to other systemic and ophthalmic antibacterials (as defined by January 2007 CLSI M100-S17 Interpretive Standards), including methicillin resistant *S. aureus*, methicillin resistant *S. epidermidis*, as well as fluoroquinolone, aminoglycoside, or macrolide resistant staphylococci and streptococci. If the combined Phase 2 and Phase 3 clinical and bacteriological outcome data indicate that sufficient isolates of pathogens resistant to other antibacterials are eradicated in ISV-403 treated infections ( $\geq 5$  cases with a  $\geq 80\%$  eradication rate or  $\geq 10$  cases with an  $\geq 50\%$  eradication rate for patients treated with ISV-403), would such data be adequate to support designation of specific antibacterial resistant organisms in the first list on the package insert for the ISV-403 product? If not, are there other criteria the FDA allows for inclusion of organisms resistant to other antibacterials in the first or second package insert lists?

**Reviewer's Comments:**

*No. A listing of organisms as sensitive to ISV-403 and resistant to other antibacterials would only be made based on clinical cures demonstrated with ISV-403 in the same organisms that demonstrated a failure to be cured with other antibacterials.*

**Meeting Comments:**

- Bausch & Lomb inquired as to how they would demonstrate clinical cures with ISV-403 in the same organisms that demonstrated a failure to be cured with other antibacterials. The Division explained that this is a comparison to another product which requires a head to head comparison demonstrating that other products failed and Bausch & Lomb's was superior.

13. B&L will submit Tier 1 QC ranges for SS734 susceptibility testing as developed by [REDACTED] b(4)  
Because systemic breakpoints will not be developed for the ISV-403 product, does FDA agree that no further development of SS734 clinical laboratory susceptibility methods or QC ranges for SS734 susceptibility testing are needed to support the NDA filing?

**Clinical Microbiology Response:** Yes.

**No Additional Meeting Comments**

14. Biochemical and genetic mechanism of action and resistance studies conducted in representative gram-positive (*S. pneumoniae*, *S. aureus*) and gram-negative (*E. coli*) pathogens (studies PHA-005 and PHA-006) confirm mechanism of action and resistance to SS734 are entirely consistent with other approved fluoroquinolone products such as ciprofloxacin, levofloxacin, gatifloxacin, moxifloxacin, and gemifloxacin. Does FDA agree that the existing molecular mechanism of action and resistance studies will be adequate to support the NDA submission and labeling for the ISV-403 product?

**Clinical Microbiology Response:** Yes.

**No Additional Meeting Comments**

15. Does FDA require any additional microbiology testing not listed in the attached microbiology summary to support the ISV-403 NDA?

**Clinical Microbiology Response:** No.

**No Additional Meeting Comments**

**Chemistry, Manufacturing, and Controls**

16. Does FDA agree with the proposal to pre-submit the CMC section of the application?

**Reviewer's comments:**

*Yes, if the CMC section is complete.*

**Meeting Comments:**

- The Division confirmed that Bausch & Lomb could pre-submit the CMC section of the application.

17. Does FDA agree with the proposed presentation of data in the CTD format?

**Reviewer's comments:**

*Yes. The eCTD format is preferred. However, if a non-eCTD electronic submission is made, it should include a table of contents with appropriate cross-file links. Note, that even in an eCTD, appropriate cross-file links can be helpful.*

**No Additional Meeting Comments**

18. Does FDA agree with the plan described to incorporate a new drug substance manufacturing site? More specifically,
- a. Does FDA agree with the selection of the starting materials?

- b. For those starting materials made in-house, would FDA expect to see flow diagrams or other details of the non-GMP portion of the process in the NDA?
- c. Does FDA agree with the proposal to ensure physical and chemical comparability of the drug substance used for Phase 3 clinical trial supplies versus that produced at the new manufacturing site?

**Reviewer's comments:**

*Yes to all questions.*

**No Additional Meeting Comments**

19. Does FDA concur with the amount of stability data available for the new manufacturing site to be provided at the time of pre-submission and the full NDA submission to support a retest date of [REDACTED] for drug substance? Note, additional data up to 12 months may be provided during the review period for drug substance made at the alternate facility; whereas, [REDACTED] data for the current IND process will be available.

b(4)

**Reviewer's comments:**

*Please ensure that the 12 months data for drug substance made at the alternate facility are provided during the review period to support the shelf life estimation.*

**No Additional Meeting Comments**

20. If B&L were to file two drug substance manufacturing sites in the NDA, could two of the drug product validation lots be made using drug substance from one manufacturing facility and the third lot from a second facility?

**Reviewer's comments:**

*Yes, if there is an appropriate demonstration of comparability of the two sources.*

**No Additional Meeting Comments**

21. Does FDA agree that one lot of the physician's sample size configuration will be sufficient to establish an expiry period and support approval of this container/closure configuration?

**Reviewer's comments:**

*Yes, and adequate stability data from the physician's sample lot are needed to establish an expiry period and approval of this container/closure configuration.*

**No Additional Meeting Comments**

22. Does FDA agree with the amount of stability data available to support a 24 month expiry for drug product?

**Reviewer's comments:**

*The adequacy of the stability data to support a 24 month expiry will be evaluated during the review process.*

**No Additional Meeting Comments**

23. Does FDA have any comment on the summary of CMC information included in the meeting package?

**Reviewer's comments:**

*As noted in the summary, the alternate synthesis is based on a single 1 kg development lot manufactured thus far. In addition to the information committed to be submitted, please provide a comparison of the impurity profiles of the drug substance made at both sites and ensure that any newly observed impurities due to the different manufacturing process are properly controlled. This comparison should include both chromatograms and tabulated data.*

**Meeting Comments:**

- Bausch & Lomb asked if it would be acceptable to use USP residual solvents limits tests. The Division advised Bausch & Lomb to submit for review a list of the solvents and the limits they are proposing to use as some are acceptable, but some are harmful to the eye. The Division will review this list and inform Bausch & Lomb of its conclusions.

**Labeling**

24. Based on the example package insert provided, does FDA have any specific recommendation for presentation of data based on the Physician Labeling Rule?

**Reviewer's comments:**

*There are no other recommendations for the presentation of data based on the Physician Labeling Rule. Please provide a desk copy of the proposed labeling in Word at the time of NDA submission to assist in formatting.*

**No Additional Meeting Comments**

**Electronic Submission**

25. Bausch & Lomb is in the process of implementing electronic systems to enable preparation and submission of eCTDs. It is anticipated according to current project plans that Bausch & Lomb will be able to submit a sample eCTD submission in October or November to FDA for review. It is possible that the review process for the sample eCTD will not be completed prior to the presubmission of the Quality and Nonclinical modules for ISV-403 (targeted for submission in December). In this situation, Bausch & Lomb proposes that the presubmission of the Quality and Nonclinical modules will be either paper or as a hybrid electronic submission (not a fully compliant eCTD).
- a) Is this acceptable?
  - b) If acceptable, how much in advance of the presubmission should Bausch & Lomb notify FDA of the format (eCTD, paper or hybrid electronic submission) for the presubmission?

**Reviewer's comments:**

- a. *It is acceptable for the presubmission of the Quality and Nonclinical modules be either paper or as a hybrid electronic submission.*
- b. *Bausch & Lomb at the time of the presubmission can notify the FDA of its format.*

***No Additional Meeting Comments***

26. Bausch & Lomb is intending for the full NDA submission to be an eCTD. Does the Division have any specific requirements for an eCTD submission that are not already defined in current Guidance for Industry?

**Reviewer's comments:**

*In Module 2, Section 2.7 Clinical Summary, subsection 2.7.2.4 Special Studies; provide all microbiology summary reports using microbiology headings / titles. This section will contain the summary reports formerly submitted in Item 7 of the NDA. Thus it contains the information used to justify the Microbiology information placed in the product package insert.*

*Provide the nonclinical-microbiology and clinical-microbiology full reports, used in the construction of the aforementioned summary reports, in Module 5 Clinical Study Reports, subsection 5.3.5.4 Other Study Reports, also using microbiology headings / titles.*

*For e-Documents (eCTD), the full study reports (Module 5) used to construct the summary reports (Module 2) should be cross-linked. All references are to be hyper-linked.*

***No Additional Meeting Comments***

**User Fee**

27. Bausch & Lomb's understanding of Sec. 736(a)(1)(B) of the Federal Food, Drug & Cosmetic Act is that payment of the NDA user fee is due upon submission of the full application, and therefore, is not due at the time of the presubmission. Please confirm this is correct.

**Reviewer's comments:**

*The NDA user fee is due at the time of the full application, not at the time of the presubmission. The PDUFA "clock" will be based at the time of the full application and at the time of payment of the user fee.*

***No Additional Meeting Comments***

**Additional Clinical Question (added 5/17/07)**

28. Bausch & Lomb has not yet fully implemented systems to produce CDISC-compliant datasets. For submission of datasets, we plan on submitting data listing datasets and analysis datasets (without programs) in SAS XPORT transport file format as well as data definition files and annotated case report forms as defined in the "Study Data Specifications" document, Version 1.3, associated with the "Guidance for Industry

Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications”.

- i) As noted above, we are planning on providing the data listing datasets and analysis datasets (without programs), but not the data tabulation datasets or subject profiles that are defined the Study Data Specifications document. Is this acceptable?
- ii) Is it acceptable to submit the data definition file in PDF format (define.pdf) rather than in XML format (define.xml)?
- iii) It is proposed that the data listing datasets and analysis datasets referenced above will be produced for only the two Phase 3 studies and Phase 2 study. For the Phase 1 studies, we would provide summary tables and data listing datasets. Is this acceptable?

**Reviewer’s comments:**

- i. No. All data sets and programs should be provided (including raw and derived data sets).*
- ii. Yes.*
- iii. The data listing datasets and analysis datasets should be produced for all Phases of the study, not just for the two Phase 3 studies and the Phase 2 study.*

**Meeting Comments:**

- Bausch & Lomb asked if CDISC-compliant datasets are required; the Division responded that they are not required, but are strongly encouraged. In addition, the Division would like to have SAS programs used to produce key efficacy and safety results.
- The Division confirmed that a horizontal standard for datasets would be acceptable.

**UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:**

- The acceptability of Bausch & Lomb’s phase 2 data as support for a NDA.

**ACTION ITEMS:**

- The Division will review the phase 2 data and provide feedback to Bausch & Lomb as to the role the data could play in supporting an NDA by August 1, 2007.
- Bausch & Lomb will prepare an alternate proposal in case the phase 2 data is not acceptable.

**ATTACHMENTS/HANDOUTS:**

None

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**This is a representation of an electronic record that was signed electronically and  
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/s/

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Edward Cox  
6/28/2007 01:48:05 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 64,335

Bausch & Lomb  
Attention: Jennifer S. Knicley  
Manager, Regulatory Affairs  
1400 North Goodman Street  
Rochester, NY 14609

Dear Ms. Knicley:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ISV-403 (0.6% SS734) Ophthalmic Suspension.

We also refer to the meeting between representatives of your firm and the FDA on December 6, 2005. The purpose of the meeting was to discuss phase 3 clinical trial designs and the overall development plans for ISV-403.

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 Alison Rodgers, Regulatory Project Manager, at (301) 796-0797.

Sincerely,

*{See appended electronic signature page}*

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

Enclosure

**MEMORANDUM OF MEETING MINUTES**

**MEETING DATE:** December 6, 2005  
**TIME:** 11:00 AM  
**LOCATION:** 10903 New Hampshire Avenue, Silver Spring, MD  
**APPLICATION:** 64,335  
**DRUG NAME:** ISV-403  
**TYPE OF MEETING:** End-of-Phase 2

**MEETING CHAIR:** Janice Soreth, M.D.

**MEETING RECORDER:** Alison Rodgers

**FDA ATTENDEES:**

**Division of Anti-Infective and Ophthalmology Products**

Janice Soreth, MD, Director  
Wiley Chambers, MD, Deputy Division Director  
Rhea Lloyd, MD, Medical Officer  
Venkat Jarugula, PhD, Clinical Pharmacology Team Leader  
Lin Qi, PhD, Chemistry Reviewer  
Martin Nevitt, MD, Medical Officer  
William Boyd, MD, Clinical Team Leader  
Connie Mahon, PhD, Clinical Microbiology Reviewer  
Amy Ellis, PhD, Pharmacology/Toxicology Reviewer  
Michael Puglisi, Project Manager  
Yan Wang, PhD, Statistical Reviewer  
Thamban Valappil, PhD, Statistical Team Leader  
Fred Marsik, PhD, Microbiology Team Leader  
Alison Rodgers, Project Manager

**EXTERNAL CONSTITUENT ATTENDEES:**

**Bausch & Lomb**

Jean-Yves Driot, Director, Toxicology  
Matthew Jonasse, Project Director  
Linda Galbier, Manager, CMC Development  
Jennifer Knicley, Manager, Regulatory Affairs  
Tim Comstock, O.D., Director, Pharmaceutical Clinical Science  
Don Handley, Director, Regulatory Affairs  
Keith Ward, Vice President, Global Preclinical Development  
Albert Sheldon, Consultant

**BACKGROUND:**

Bausch & Lomb requested an End-of-Phase 2 meeting to discuss the Phase 3 clinical trial designs and overall development plan for ISV-403. A meeting package was submitted on November 7, 2005. The division provided responses to the questions outlined in the

briefing package via facsimile on December 1, 2005. The meeting served to clarify those responses.

**GENERAL COMMENTS:** The questions from the background package are restated below in bold. Each question is then followed by the FDA comments in italics. These are identical to the comments provided to Bausch & Lomb on December 1, 2005, via facsimile. These comments are followed by bulleted meeting discussion points.

**Clinical**

- 1. In the two draft Phase 3 protocols, B&L #433 and B&L #434, the proposed visit schedule is Day 1, Day 4±1 day and Day 8+1 day, allowing 48 hours after the last dose, with the primary efficacy endpoints (clinical resolution and eradication of baseline bacterial infection) being at Day 8. Does the Agency concur with this visit schedule?**

**FDA Response:**

*Bacterial conjunctivitis is a self-limiting condition. There is less likelihood that a significant clinical benefit will be observed at later time periods when comparing the drug to vehicle. Therefore, we recommend that Visit 2 (Day 4 ± 1) be the primary endpoint in both studies, while continuing the study out to Day 8.*

*For labeling down to the age of 1 year, trials should be conducted in at least 5 one-year old patients.*

*Endothelial cell counts should be performed at baseline and at the end of the trial in one study.*

*For multi-center trials, there should be at least 10 patients per arm per site so that tests for investigator interaction can be performed.*

*The finalized protocols will be reviewed upon submission and any additional comments will be sent to the sponsor.*

**Meeting Discussion Points:**

- Bausch & Lomb stated that they have not seen endothelial cell counts for other fluoroquinolones.
  - The Division responded that endothelial cell counts are required during development of all topical ophthalmic drug products. The test should be done on a subset of at least 100 patients who are on the drug and not placebo. The subjects do not have to be conjunctivitis patients.
- 2. Does the Agency have any comment on the study design, inclusion/exclusion criteria, study procedures, clinical assessments, efficacy and safety endpoints,**

**or statistical methods proposed in the draft Phase 3 protocols, B&L #433 and B&L #434?**

FDA Response:

*Refer to response to question 1.*

*In addition, the Agency expects to see an "a true Intent-to-Treat with the last observation carried forward for missing data" analysis. While it is recognized that many of the patients in this analysis may not have bacterial conjunctivitis, it is expected that the drug group will not be inferior to the vehicle group in this analysis. Superiority of the drug product over vehicle is only expected in patient populations with positive bacterial cultures at baseline. The "Per Protocol using only observed data" is expected to be the primary analysis with any additional analyses as needed to establish the robustness of the findings.*

Meeting Discussion Points:

- Bausch & Lomb asked if the Intent-to-Treat trial applies to vehicle controlled trials.
- The Division responded yes; it does not want a product that is inferior to vehicle.

*For protocol #434 Section 11.1:*

*In the statistical analysis it is recommended that the null and alternate hypotheses be set at -0.15 for all analyses, not -0.10 and -0.20 as proposed.*

- 3. Does the Agency agree that the study designs and plan for conduct of the proposed adequate and well-controlled Phase 3 trials, if completed successfully, will comprise appropriate evidence to support the proposed indication and labeling as drafted in the attached Target Product Profile?**

FDA Response:

*In principle yes, however, the results of the studies will need to be reviewed prior to making determinations regarding labeling.*

*For the Target Product profile, in-vivo rates will be used to determine the contents of the indication section of the labeling. Criteria for consideration of including in the labeling are:*

- *Organisms that are cultured from an eye with conjunctivitis and treated with the drug in a clinical trial in 5 or more cases with a  $\geq 80\%$  eradication rate\* or cultured from an eye with conjunctivitis and treated with the drug in a clinical trial in 10 or more cases with a  $\geq 50\%$  eradication rate. Organisms identified from the first category are usually identified in labeling with an asterisk.*

- *Organisms that are cultured in less than 5 infections are not listed in the label.*

Meeting Discussion Points: No further comment.

4. **In the proposed Phase 3 trials, Bausch & Lomb intends to enroll patients who are at least one year of age. As previously indicated by the Division (January 29, 2003 response to the pre-IND meeting package), we must enroll at least five one-year old patients to assure labeling down to the age of 1 year.**
  - a. **Does the Agency have any additional guidance specific to total number of pediatric patients and age distribution, to fulfill all pediatric requirements under the Pediatric Research Equity Act?**

FDA Response:

*We expect for investigators to make an effort to get a visual acuity measurement in all patients. Lea symbols are acceptable for those patients that cannot reliably use a Snellen or ETDRS eye chart.*

Meeting Discussion Point:

- Bausch & Lomb asked if the requirement for five one-year old patients is the only specific requirement regarding the number of patients. The FDA responded affirmatively.

**b. Is it acceptable to include pediatric subjects from the Phase 2 trial to fulfill the pediatric requirement?**

FDA Response:

*Acceptable as long as the inclusion criteria, protocols, etc., are not significantly different.*

Meeting Discussion Points: No further comments.

**c. What, if any, additional requirements would need to be fulfilled should Bausch & Lomb wish to seek pediatric exclusivity?**

FDA Response:

*Bausch & Lomb should request that the Agency issue a Pediatric Written Request Letter.*

Meeting Discussion Point:

- The Division asked if Bausch & Lomb wanted a Pediatric Written Request Letter. The Division noted that only neonatal conjunctivitis letters had been written for

conjunctivitis and a neonatal conjunctivitis letter would be required for this product.

- Bausch & Lomb stated that they would respond to the Division regarding the letter at a later date.
5. **Based on the plasma levels of SS734 observed in the Phase 1 clinical study (C-02-403-001) as summarized in this meeting package (Tab 5), and assuming that inflammation does not result in a large increase in systemic exposure in the proposed animal study (Tab 6), does the Agency concur that no additional human pharmacokinetic data would be required to support a new drug application?**

FDA Response:

*No. Since this is an NME, the sponsor is recommended to collect blood samples in a subset of patient population in one of the phase 3 studies and determine the systemic absorption in the presence of bacterial conjunctivitis.*

Meeting Discussion Points:

- Bausch & Lomb stated they are in agreement that pharmacokinetic data would be useful data to have. However, they noted that there are logistical issues in trying to collect this data in Phase 3 trials and they would like to do a separate study to collect the pharmacokinetic data.
- The Agency responded that a separate study would be acceptable provided the patients studied have the signs and symptoms of conjunctivitis. In addition, 20 patients should be included in the study.

Preclinical

6. **Per the rationale submitted on October 27, 2005 (S-0021), is it acceptable to waive carcinogenicity studies for this product?**

FDA Response:

*Carcinogenicity studies will not be necessary for this product.*

Meeting Discussion Points: No further comment.

7. **As noted in the pharmacokinetics section of the Clinical Data Summary (Tab 6), Bausch & Lomb plans to conduct a study evaluating the ocular pharmacokinetics and systemic exposure of SS734 following a single instillation of ISV-403 in pigmented rabbits with or without corneal inflammation (draft protocol provided under Tab 6). This study will provide data on the effect of inflammation on absorption in response to the comment provided by the Agency on May 24, 2004 in response to our End of Phase 1 meeting request.**

**a. Does the Agency have any comment on the design of the planned study?**

FDA Response:

*The pharmacology/toxicology reviewer and clinical team do not believe that this study is necessary and recommend that it not be conducted.*

Meeting Discussion Points: No further comment.

**b. Does the Agency concur that the planned study will be sufficient to address the effect of inflammation on absorption?**

FDA Response:

*The rabbit study is not likely to provide data that will have any bearing on how this product is used in the clinic, nor will it provide any information that is relevant to how the product would be labeled or regulated.*

**8. Are the completed studies summarized in the Preclinical Summary adequate to support initiation of the Phase 3 clinical trials?**

*FDA Response:*

*Yes, they appear to be.*

Meeting Discussion Points: No further comment.

**9. What, if any, additional preclinical studies are required for an NDA submission?**

FDA Response:

*At this time, we do not anticipate that additional nonclinical studies will be needed to support an NDA submission for ISV-403 other than those planned by the sponsor.*

Meeting Discussion Points: No further comment.

Microbiology

**10. Bausch & Lomb would like to include a second list of organisms in the Microbiology subsection of the ISV-403 package insert based on in vitro susceptibility data, similar to other approved ophthalmic fluoroquinolones. We realize that the algorithm used by the Agency to construct the second list is usually contingent on systemic breakpoints. Since systemic breakpoints are not available for this product because there is no systemic product, we would like to propose an alternate analysis. Is it acceptable to use the highest MIC**

**successfully treated for a species within a genus to allow inclusion of other species within that genus? For example, if *Staphylococcus aureus* is approved and listed in the indications section, and the highest MIC treated successfully is 0.125 mcg/mL, can we use this value as a "breakpoint" to determine whether other staphylococcal species have MIC 90 less than or equal to 0.125 mcg/mL for inclusion in the second list?**

FDA Response:

*There is no requirement to include a "second list" of microorganisms. If a "second" list is proposed, it should be based on the same algorithm used for other approved ophthalmic drug products.*

Meeting Discussion Points:

- Bausch & Lomb asked about the algorithm used for ophthalmic products.
- The Division responded that it is the algorithm written years ago for systemic anti-infectives. Bausch & Lomb noted that this algorithm does not appear to have been followed.
- The Division explained that while it follows this algorithm, it is just guidance.
- Bausch & Lomb asked if they should submit a position paper or proposal in support of their request to use a different process to establish an ophthalmic second list. The Division responded that it would be willing to review this.
- Bausch & Lomb stated that they would submit this paper within the next two months.
- Bausch & Lomb noted that they expect to finish Phase 3 trials by mid to late 2007.

**11. Will the data generated to date and the studies planned for Phase 3 be sufficient to support inclusion of the statements intended for the Microbiology section of the package insert as shown in the Target Product Profile?**

FDA Response:

*This cannot be determined until the clinical trials are completed.*

Meeting Discussion Points:

- The Division suggested Bausch & Lomb consider adding gram stains to the protocol. Bausch & Lomb will consider this suggestion. The Division will discuss further internally as there was not uniform agreement on this request.
- Bausch & Lomb noted that it plans to start trials in the first quarter of 2006.

**Chemistry, Manufacturing, and Controls**

- 12. Does the Agency agree that the proposed manufacturing, controls and specifications for drug substance and drug product as presented in the CMC Summary are sufficient for the clinical batches to be used in the Phase 3 trials?**

**FDA Response:**

*It is recommended that photostability testing be performed on at least one batch of drug product because the drug substance is photodegradable (See ICH Q1B for testing conditions).*

**Meeting Discussion Points: No further comment.**

- 13. Sections S.7 (SS734 Drug Substance) and P.8. (ISV-403; Placebo to ISV-403; Comparator Drug Product) of the CMC Summary contain outlines of the stability studies to be conducted on batches to be used in the Phase 3 trials. Does the Agency agree that the proposed stability studies are sufficient to support Phase 3?**

**FDA Response:**

*he proposed stability studies are sufficient to support Phase 3.*

**Meeting Discussion Points: No further comment.**

- 14. The stability studies outlined for the Phase 3 clinical batches of ISV-403 are intended to provide the primary stability data for the NDA. As noted in the CMC Summary, Bausch & Lomb intends to store 3 batches of drug product packaged in labeled bottles in the upright and horizontal positions. One of the 3 batches will also be packaged with a mock carton and insert in the upright and horizontal positions. Does the Agency concur with this plan?**

**FDA Response:**

*Please include a description of sampling protocol in the proposed plan. It is recommended that acceptance criteria for density, particle size analysis, and weight loss be established and provided in the coming NDA.*

- 15. Does the Agency have any comments on the information in the CMC Summary included in the meeting package?**

**FDA Response:**

*Please explain why SS734 (an 8-chloro fluoroquinolone) is described as an 8-methoxy fluoroquinolone in the Target Product Profile. Please provide complete information on*

both drug substance and drug product in the coming NDA if DMF [REDACTED] is transferred to Bausch & Lomb. In the coming NDA, provide acceptance criteria for EDTA assay, density, and particle size analysis in the drug product specification. b(4)

With regard to the manufacturing process, the submission is not clear as to the critical parameters to be used for sterilization of the drug product. Specifically, the flow diagram on page 273 of the submission states [REDACTED], but does not provide details as to the sterilization [REDACTED]. Further, the same flow diagram demonstrates the [REDACTED] [REDACTED] however it does not state how these components are sterilized [REDACTED]. This information should be provided. b(4)

Meeting Discussion Points:

- Bausch & Lomb noted that the description of SS734 as an 8-methoxy fluoroquinolone in the Target Product Profile was a typographical error.
- Bausch & Lomb stated that it will address and update the information regarding the critical parameters to be used for sterilization of the drug product in a Phase 3 amendment.

**ACTION ITEMS:**

- Bausch & Lomb will submit a position paper in support of their request to use a different process to establish an ophthalmic second list.
- The Division will review this request and respond to Bausch & Lomb.
- The Division will have internal discussions regarding the need for adding gram stains to the protocol.

Signature of Meeting Recorder:

\_\_\_\_\_  
Alison Rodgers  
Project Manager  
Division of Anti-Infective and Ophthalmology Products

Signature of Meeting Chair:

\_\_\_\_\_  
Janice M. Soreth, M.D.  
Director  
Division of Anti-Infective and Ophthalmology Products

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Lillian Gavrilovich  
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Signing for Dr. Janice Soreth.

## Rodgers, Alison

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**From:** Greeley, George  
**Sent:** Wednesday, March 11, 2009 8:25 AM  
**To:** Rodgers, Alison  
**Cc:** Mathis, Lisa  
**Subject:** NDA 22-308 Besivance

**Importance:** High

Hi Alison,

The Besivance (besifloxacin hydrochloride ophthalmic suspension) partial waiver and assessment was reviewed by the PeRC PREA Subcommittee on July 30, 2008. The Division recommended a partial waiver from 0 to 1 month because the disease/condition does not exist in children. Efficacy was extrapolated from 1 month to 12 months and studies were completed from 1 year to 16 years. The PeRC agreed with the Division to grant a partial waiver as well as the extrapolation and assessment for this product.

Thank you.

George Greeley  
Regulatory Health Project Manager  
Pediatric and Maternal Health Staff  
Office of New Drugs  
FDA/CDER  
10903 New Hampshire Ave.  
Bldg #22, Room 6467  
Silver Spring, MD 20993-0002  
301.796.4025

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**Rodgers, Alison**

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**From:** Rodgers, Alison  
**Sent:** Tuesday, March 03, 2009 9:25 AM  
**To:** 'Knicley, Jennifer S'  
**Subject:** NDA 22-308 - Carton and Container Labels

Dear Jennifer,

Regarding the besifloxacin carton and container labels:

The established name should be revised on the carton and container labels to a font size that is at least half as large of that of the proprietary name and a prominence commensurate with the proprietary name, as stated in 21 CFR 201.10(g)(2).

Please revise the labeling accordingly.

Please confirm receipt of this email.

Thank you,

Alison

Alison K. Rodgers  
Regulatory Health Project Manager  
FDA/CDER  
Division of Anti-Infective and Ophthalmology Products  
Phone: 301-796-0797  
Fax: 301-796-9882  
Email: [alison.rodgers@fda.hhs.gov](mailto:alison.rodgers@fda.hhs.gov)

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Alison Rodgers  
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CSO

Alison Rodgers  
3/3/2009 09:28:47 AM  
CSO

**Rodgers, Alison**

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**From:** Rodgers, Alison  
**Sent:** Tuesday, October 07, 2008 1:55 PM  
**To:** 'Knicley, Jennifer S'  
**Subject:** IND 64,335/ NDA 22-308 - Trade Name

Hi Jennifer,

Unfortunately, we object to the use of the proprietary name, Optura. Please see the comments below:

The findings of our Proprietary Name Risk Assessment indicate that the proposed name, Optura, is vulnerable to name confusion that could lead to medication errors with Optivar and Optive. As such, the Division of Medication Error Prevention and Analysis objects to the use of the proprietary name, Optura, for this product.

***Labels and Labeling***

**1. Container Labels**

- a. To address the inconsistency in representing the product strength (i.e. besifloxacin hydrochloride 0.6% as base vs. besifloxacin 0.6%), the applicant should follow USP guidelines for the naming format of the drug product (USP, General Chapter Nomenclature <1121>). The recommended naming format is besifloxacin 0.6% and besifloxacin ophthalmic suspension 0.6%, as applicable.
- b. Replace the patent numbers on the 2 mL container label with the storage and usual dosage information.

**2. Carton Labeling**

- a. To address the inconsistency in representing the product strength (i.e. besifloxacin hydrochloride 0.6% as base vs. besifloxacin 0.6%), the applicant should follow USP guidelines for the naming format of the drug product (USP, General Chapter Nomenclature <1121>). The recommended naming format is besifloxacin 0.6% and besifloxacin ophthalmic suspension 0.6%, as applicable.
- b. Relocate the "For Ophthalmic Use Only" information to the principal display panel so that it is prominently displayed. To allow adequate space, decrease the prominence of the graphic representation on the principal display panel. This will also allow for the established name and strength to be increased in size.

Please submit an alternate name at your earliest convenience.

Please let me know if you have questions.

Thank you,  
Alison

Alison K. Rodgers  
Regulatory Health Project Manager  
FDA/CDER  
Division of Anti-Infective and Ophthalmology Products  
Phone: 301-796-0797  
Fax: 301-796-9882

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**Rodgers, Alison**

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**From:** Rodgers, Alison  
**Sent:** Tuesday, January 27, 2009 9:11 AM  
**To:** 'Knicley, Jennifer S'  
**Subject:** NDA 22-308 January 23, 2009 Amendment

**Importance:** High

Hi Jennifer,

Please note:

*In your amendment of January 23, 2009, regarding a test for leachables, you state, "The FDA agreed that this test could be performed on stability only." This is not correct. We agreed only that it should be done on stability, not that it could be excluded from release testing.*

*As stated in our initial request "...a test and acceptance criterion for leachables in the product should be set at NMT [REDACTED] While we recognize that the current HPLC procedure for impurities may not be specific for all extractables, we think it provides reasonable assurance of the absence of most extractables, both known and new.*

**b(4)**

Please respond as soon as possible.

Please let me know if you have any questions.

Thank you,

Alison

Alison K. Rodgers  
Regulatory Health Project Manager  
FDA/CDER  
Division of Anti-Infective and Ophthalmology Products  
Phone: 301-796-0797  
Fax: 301-796-9882  
Email: alison.rodgers@fda.hhs.gov

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CSO

Alison Rodgers  
2/17/2009 02:58:04 PM  
CSO

**Rodgers, Alison**

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**From:** Rodgers, Alison  
**Sent:** Tuesday, January 13, 2009 10:01 AM  
**To:** 'Knicley, Jennifer S'  
**Subject:** NDA 22-308 - Response to Chemistry IR 9-3-08  
**Importance:** High

Hi Jennifer,

Please note our comment listed below. We really need to receive your response as soon as possible, preferably this week. Please submit your response to the NDA and send a copy to me. Please let me know if you have questions.

**The response to previous FDA Question #1 dated 9/3/08 is inadequate. Although the specification's proposed acceptance criterion of NMT [redacted] or any unspecified drug-related impurity is acceptable, a test and acceptance criterion for leachables in the product should be set at NMT [redacted]. We do not believe that leachable testing of initial lots is adequate to provide continuing assurance of product quality.**

**b(4)**

Thank you,

Alison

Alison K. Rodgers  
Regulatory Health Project Manager  
FDA/CDER  
Division of Anti-Infective and Ophthalmology Products  
Phone: 301-796-0797  
Fax: 301-796-9882  
Email: [alison.rodgers@fda.hhs.gov](mailto:alison.rodgers@fda.hhs.gov)

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