Rodgers, Alison

From: Rodgers, Alison
Sent: Tuesday, December 02, 2008 10:51 AM
To: 'Knicley, Jennifer S'
Subject: NDA 22-308 - Request for Microbiology Information 12-02-08

Hi Jennifer,

Please see the request for Microbiology information regarding NDA 22-308 listed below. Please let me know when you plan to respond. Your response should be submitted to the NDA. Please let me know if you have any questions.

Thank you,

Alison

1. Please clarify and correct Table 29 in Section 2.7.2 of the Application. This table summarizes the data from all in vitro investigations of besifloxacin antimicrobial activity. Specific discrepancies include (but are not limited to) the following:
   a. In Row 3, the "organism" column identifies "CDC coryneform group G" (*C. pseudodiphtheriticum* and *C. striatum*). The referenced study [redacted] 99K3020B), however, only lists the more general classification "*Corynebacterium* species" in the data tables. Please state whether identification to species level was performed on these isolates. If that identification was performed, please list MIC_{90} and MIC_{range} for each species identified, and please include a complete description of the method used to identify these isolates. Since this is the only presented data that describes besifloxacin in vitro activity against *Corynebacterium* species, a line listing (including species identification, MIC against each antimicrobial tested, specimen source, specimen collection date) would be valuable for review purposes. b(4)
   b. In Row 9, the "Organism" column appears to identify all Staphylococcus aureus isolates tested in all in vitro investigations, summarized in this table. If that is the case, please review and make the appropriate corrections to all column entries (all are erroneous, with the possible exception of the right-most column). If that is not the case, please clarify the meaning of the "Organism" column for that data row.
   c. In Row 28, the "Organism" column lists "*Streptococcus mitis* group." Since members of this group are sought individually as indications for besifloxacin (and *Streptococcus oralis*, presumably included in the *S. mitis* group, is listed again in the following row) please subdivide this column to list antimicrobial activity for each species tested in Study 500421 (the single study referenced for this group of ophthalmic pathogens).
   d. In the footnotes, please include a definition for each resistance phenotype described in the table. The definition should include the breakpoint values used to define the particular phenotype (e.g. "penicillin-resistant *Streptococcus pneumoniae*": penicillin (nonmeningitis) $\geq$ 8 µg/ml).
   e. Please make any additional corrections or clarifications, as appropriate.

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

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

/s/

Alison Rodgers
12/2/2008 10:54:57 AM
CSO

Alison Rodgers
12/2/2008 10:55:41 AM
CSO

Rodgers, Alison

From: Rodgers, Alison
Sent: Tuesday, October 21, 2008 11:30 AM
To: 'Knicley, Jennifer S'
Subject: NDA 22-308 CMC Information Request 10-21-08

Hi Jennifer,

Please see the CMC request for information below. Please let me know when you plan to respond. Please submit your response to the NDA.

1. Regarding the drug product container closure, a beige cap is noted for the drug product. Please confirm that this product should meet the AAO code: [redacted] color (tan) for an anti-infective drug product. b(4)

2. Regarding the analytical method for the drug substance and drug product, please provide a system suitability test that includes a standard at the quantitation limit to ensure detectability of impurities at that level. The system suitability test should be included for both drug substance and drug product impurities test.

3. The stability protocol does not contain an adequate commitment. It should state to inform the division and to reference the CFR for FDA contact in case of failure. It should state that if evidence exists that the deviation is a single occurrence that does not affect the safety and efficacy of the drug product, the applicant should immediately discuss it with the reviewing division and provide justification for the continued distribution of that batch. The change or deterioration in the distributed drug product is reported as per 21 CFR314.81(b)(1)(ii).

4. Please provide information on how much and when will stability update be provided for the product stability batches made with drug substance from [redacted] b(4)

Please let me know if you have any questions.

Also, 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

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

/s/

Alison Rodgers
10/21/2008 11:32:16 AM
CSO

Alison Rodgers
10/21/2008 11:32:44 AM
CSO

Rodgers, Alison

From: Rodgers, Alison
Sent: Friday, October 10, 2008 1:20 PM
To: 'Knicley, Jennifer S'
Subject: NDA 22-308 - Request for Information 10-10-08

Hi Jennifer,

A sterility assurance review of NDA 22-308 is on-going. Please provide the following information, or reference to its location in the subject submission:

- The methods used and data sets from the 1997 and 2004 container closure integrity tests.
- A narrative describing the environmental microbiological monitoring program which includes information regarding the sampling and testing methods, incubation conditions, alert and action limits and routine production monitoring frequency.
- [redacted] b(4)
- A description of the method used for sterility testing along with verification data that the sterility test method is suitable for use with the subject drug product.
- A description of the method used for bacterial endotoxins testing along with verification data that the bacterial endotoxins test method is suitable for use with the subject drug product (reference to 03 SEP 2008 electronic mail from the Agency to the applicant regarding the addition to the drug product specification of an endotoxin test method and an acceptance criterion).

Please let me know when you will submit your response to the NDA. 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

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

/s/

Alison Rodgers
10/10/2008 01:26:42 PM
CSO

Rodgers, Alison

From: Rodgers, Alison
Sent: Friday, October 10, 2008 8:39 AM
To: 'Knicley, Jennifer S'
Subject: FW: NDA 22-308 - Request for Information 10-08-08

Hi Jennifer,

Please provide a response to our request for the 95% Confidence Intervals for the CMH test for Clinical Resolution for the Safety, Per Protocol, and Modified Intent to Treat populations for Visits 2 and 3 in your submission, even if you cannot provide the information.

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
Email: alison.rodgers@fda.hhs.gov

From: Rodgers, Alison
Sent: Thursday, October 09, 2008 9:09 AM
To: 'Knicley, Jennifer S'
Subject: NDA 22-308 - Request for Information 10-08-08

Hi Jennifer,

Please see our request for information listed below:

The following requested information pertains to Study # 373:

The clinical reviewer is unable to locate the Clinical Resolution results for Visit 2 (Day 4 +/- 1 day) for either the Safety or the Per Protocol populations in Study #373. Please provide where this information can be found within the NDA submission, or if not submitted, please submit.

Additionally, a) please provide the 95% Confidence Intervals for the CMH test for Clinical Resolution for the Safety, Per Protocol, and Modified Intent To Treat populations for Visits 2 and 3.
b) please provide the unadjusted p values and their 95% Confidence Intervals for Clinical Resolution for the Safety, Per Protocol, and Modified Intent To Treat populations for Visits 2 and 3.

Please respond by submitting your response to the NDA and to me via email as soon as possible.

Please let me know if you have any questions.

Thank you,

Alison

Alison K. Rodgers
Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products
Center for Drug Evaluation and Research

Phone: 301-796-0797
Fax: 301-796-9882

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

/s/

Alison Rodgers
10/10/2008 08:43:43 AM
CSO

Alison Rodgers
10/10/2008 08:44:09 AM
CSO

Rodgers, Alison

From: Rodgers, Alison
Sent: Thursday, October 09, 2008 9:09 AM
To: 'Knicley, Jennifer S'
Subject: NDA 22-308 - Request for Information 10-08-08

Hi Jennifer,

Please see our request for information listed below:

The following requested information pertains to Study # 373:

The clinical reviewer is unable to locate the Clinical Resolution results for Visit 2 (Day 4 +/- 1 day) for either the Safety or the Per Protocol populations in Study #373. Please provide where this information can be found within the NDA submission, or if not submitted, please submit.

Additionally, a) please provide the 95% Confidence Intervals for the CMH test for Clinical Resolution for the Safety, Per Protocol, and Modified Intent To Treat populations for Visits 2 and 3.
b) please provide the unadjusted p values and their 95% Confidence Intervals for Clinical Resolution for the Safety, Per Protocol, and Modified Intent To Treat populations for Visits 2 and 3.

Please respond by submitting your response to the NDA and to me via email as soon as possible.

Please let me know if you have any questions.

Thank you,

Alison

Alison K. Rodgers
Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products
Center for Drug Evaluation and Research
Phone: 301-796-0797
Fax: 301-796-9882

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

/s/

Alison Rodgers
10/9/2008 09:19:01 AM
CSO

Alison Rodgers
10/9/2008 09:19:38 AM
CSO

Rodgers, Alison

From: Rodgers, Alison
Sent: Tuesday, September 16, 2008 12:02 PM
To: 'Knicley, Jennifer S'
Subject: RE: NDA 22-308 - Request for Chemistry Information

Attachments: Picture (Enhanced Metafile)

Hi Jennifer,

Please note our clarification to question # 10 below. Please let me know if you need more information.

Thanks,

Alison

Clarification to #10

The reviewer noted that some impurities are increased in the batch summary pasted below. For example, the impurity @RRT [redacted] and total impurities are somewhat higher at release than in the primary batches. The reviewer is unsure if the impurity/degradant cited in #10 (it contains a " [redacted] moiety) is changed or not because earlier table might not be as updated as this table below. If you confirm that" [redacted] is not present in DS batches produced at " [redacted] site during its initial release or during later stability cycle, then there is no need for further explanation to IR #10. b(4)

Table 3.2.S.4.4-6: Related Substances Results for Primary Stability Batches vs. Lots Made at Proposed Commercial Site [redacted]

[redacted] b(4)

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

From: Knicley, Jennifer S [mailto:Jennifer_Knicley@bausch.com]
Sent: Friday, September 12, 2008 2:52 PM
To: Rodgers, Alison
Subject: RE: NDA 22-308 - Request for Chemistry Information

Hi Alison,

In order to appropriately respond to all the questions below, we would like to seek some additional clarification on question #10 below.

10. Please explain why the drug substance manufactured in " [redacted] has different level of impurity b(4)

identified as the ' [redacted] Is this impurity adequately qualified? b(4)

What is the RRT of this impurity on the HPLC method?

Request for clarification: As noted in Table 3.2.S.3.2-2 of the NDA, the ' [redacted] is identified only as a potential degradation product resulting from [redacted]. This potential degradant has not been observed in the drug substance to date. Please clarify why it is noted that this impurity is found at different levels in the [redacted] material and why the impurity should be qualified. b(4)

Thank you,
Jennifer

From: Rodgers, Alison [mailto:Alison.Rodgers@fda.hhs.gov]
Sent: Wednesday, September 03, 2008 12:50 PM
To: Knicley, Jennifer S
Subject: NDA 22-308 - Request for Chemistry Information

Hi Jennifer,

Please see the request for Chemistry information regarding Besifloxacin HCl Ophthalmic Suspension 0.6% below. Please let me know when you plan to respond. Please submit your response to the NDA. Please contact me if you have questions.

Thank you,

Alison

NDA 22-308
Besifloxacin HCl Ophthalmic Suspension 0.6% as base

1. Please add a [redacted] to the test and acceptance criteria for particle size testing for the drug substance and drug product specifications.

2. The impurities/degradation products should be listed in the drug product specification as follows:
   Each specified identified leachable in ppm
   Each specified unidentified leachable in ppm
   Total leachables in ppm
   Each specified identified degradation product in %
   Each specified unidentified degradation product in %
   Any individual unspecified impurity at NMT [redacted]
   Total impurities

3. a) Please describe the final package of the product including secondary packaging, for example, will carton be used? If a label is glued to bottle, please provide the type of adhesive used and provide all of its components. If the label is printed on the container, please describe type of ink used, and volatile components that has potential for migration through LDPE.

   b) Provide stability data that [redacted] label printing ink and other ink) and (label adhesive) will not penetrate the container for the shelf life of the product. Please provide regulatory information indicating that printing inks and label adhesive for the bottles are suitable for use as packaging components.

4. Please ensure that all processing impurities are either absent or controlled in the final drug substance.

Please list all potentially toxic impurities in the drug substance batches and the level qualified. Is [redacted] absent in the final drug substance? b(4)

5. Endotoxin test and acceptance criteria should be provided in the final drug product.

6. Provide a comparison of the manufacturing differences between the [redacted] site and the [redacted] site. b(4)

7. Provide actual values observed instead of proposed residual limit (e.g. < 1ppm) for [redacted] of the package components as indicated on Table 3.2.P.3.5.26: Residue results for the 1X full [redacted] cycle. Explain how the acceptance criteria for [redacted] and related residues were determined. b(4)

8. Please provide an updated table listing all the impurities and degradants cited in the following two tables for the drug substance batches manufactured in the [redacted] site. If higher levels of impurities have been found, please justify the higher level and ensure that the acceptance criteria are within safety levels qualified. Please list all identified impurities by chemical name and list unidentified impurities by RRT along with safety level qualified. Please add a column indicating whether the impurity has seen observed. b(4)
   Table 3.2.S.3.2-2: Structures of Potential Drug Related Degradation Products
   Table 3.2.S.3.2-1: Structures of Potential Impurities of Besifloxacin HCl

9. The three lots of stability data reported for drug substance manufactured at [redacted] are small (about 3 kg batches). What will be commercial lot size proposed at this site? b(4)

10. Please explain why the drug substance manufactured in [redacted] has different level of impurity identified as the [redacted] Is this impurity b(4)
    adequately qualified?
    What is the RRT of this impurity on the HPLC method?

11. FDA recommends that the name of the drug in the label matches the strength in all labelings: Please make the following change in the labels:

    Besifloxacin HCl Ophthalmic Suspension as 0.6% base.
    to
    Besifloxacin Ophthalmic Suspension 0.6%.

A statement may be added to declare that the drug is a hydrochloride salt as appropriate if needed, but the established name should be Besifloxacin Ophthalmic Suspension.

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

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

/s/

Alison Rodgers
9/16/2008 12:57:42 PM
CSO

Alison Rodgers
9/16/2008 12:57:57 PM
CSO

Rodgers, Alison

From: Rodgers, Alison
Sent: Friday, July 11, 2008 9:42 AM
To: 'Knicley, Jennifer S'
Subject: NDA 22-308 Information Request 07-11-08

Hi Jennifer,

Please see the request for information regarding NDA 22-308 listed below. Please let me know when you plan to respond. Please submit your response to the NDA.

Thank you,

Alison

Information Request:

1) Statistics: Please provide the SAS programs for generating efficacy and safety results for the Phase 2 study 373, and the two pivotal studies, study 433, and study 434.

2) Microbiology: Establish a finished product bacterial endotoxins specification. Provide appropriate qualification data demonstrating the suitability of the chosen test method to detect bacterial endotoxins in the subject drug product. Reference is made to USP<85>.

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

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

/s/

Alison Rodgers
7/11/2008 09:46:13 AM
CSO

Alison Rodgers
7/11/2008 09:46:38 AM
CSO

Rodgers, Alison

From: Rodgers, Alison
Sent: Wednesday, February 27, 2008 12:28 PM
To: 'Knicley, Jennifer S'
Subject: NDA 22-308 - CMC Request for Information 02-28-08

Hi Jennifer,

Please note the CMC questions regarding NDA 22-308 listed below. Please submit your response to the NDA and forward a copy to me via email if possible.

Does the contract sterilization site [redacted] perform release tests of the bottle, tip and cap? If so, please list the tests or refer to the location in the NDA. Is the residual [redacted] test performed at [redacted] or at another site? b(4)

Please contact me 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

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

/s/

Alison Rodgers
2/27/2008 12:31:46 PM
CSO

Rodgers, Alison

From: Rodgers, Alison
Sent: Monday, February 04, 2008 12:41 PM
To: 'Knicley, Jennifer S'
Subject: NDA 22-308 CMC Information Request 02-04-08

Attachments: Picture (Metafile)

Hi Jen,

[redacted] b(4)

Our chemist is trying to determine the "profile class" of the manufacturing site (CFN [redacted] above. Please respond to the following two questions regarding this site: b(4)

1. How is the referenced "packaging component" sterilized (e.g. Gas, radiation, heat etc?)
2. What is the " packaging component sterilized" (stopper, cap, container or secondary package?)

Please let me know when you plan to respond. Please submit your response to the NDA. Do not hesitate to contact me 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

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

/s/

Alison Rodgers
2/4/2008 12:45:11 PM
CSO

Rodgers, Alison

From: Rodgers, Alison
Sent: Wednesday, January 16, 2008 9:19 AM
To: 'Knicley, Jennifer S'
Subject: RE: Clinical microbiology questions

Hi Jennifer,

Responses to your questions are listed below. Please let me know if you need additional information.

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

From: Knicley, Jennifer S [mailto:Jennifer_Knicley@bausch.com]
Sent: Monday, January 14, 2008 9:49 AM
To: Rodgers, Alison
Subject: Clinical microbiology questions
Importance: High

Re: NDA 22-308 Besifloxacin HCl Ophthalmic Suspension, 0.6%

Hi Alison,

In putting together our data for the upcoming NDA submission (Clinical/Micro sections), our team has come up with some questions regarding presentation of the clinical microbiology data. We are hoping the Division can provide some guidance on their expectations with respect to the following topics.

1. For the modified intent to treat population within the clinical tables, subjects are being analyzed under the treatment to which they were randomized (in case there is a difference between randomized and actual treatment). Should the microbiological MIC data tables analyze subjects similarly (as randomized) or should they analyze subjects as treated?

FDA Response: Analyze data as treated.

2. For the primary data set of MIC data from isolates obtained from our clinical trials, does FDA expect to see SAS transport file format or Microsoft Excel data sets?

FDA Response: SAS transport file.

Thank you.
Jennifer

Jennifer S. Knicley
Manager, Global Regulatory Affairs
Pharmaceuticals
Bausch & Lomb, Inc.
1400 North Goodman Street
Rochester, NY 14609
Tel: 585-338-6307
Fax: 585-338-0700

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

/s/

Alison Rodgers
1/16/2008 09:29:10 AM
CSO

Alison Rodgers
1/16/2008 09:29:27 AM
CSO

NDA/BLA REGULATORY FILING REVIEW

(Including Memo of Filing Meeting)

Application Information		
NDA # 22-308 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: OPTURA Established/Proper Name: besifloxacin hydrochloride ophthalmic suspension Dosage Form: Topical Strengths: 0.6%		
Applicant: Bausch & Lomb, Inc. Agent for Applicant (if applicable):		
Date of Application: May 30, 2008 Date of Receipt: June 2, 2008 Date clock started after UN:		
PDUFA Goal Date: April 2, 2009	Action Goal Date (if different):	
Filing Date: August 1, 2008 Date of Filing Meeting: July 9, 2008		
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1		
Proposed Indication(s): treatment of bacterial conjunctivitis		

Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***Refer to Appendix A for further information.***	X 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease Priority review voucher was submitted, review classification defaults to Priority.***	X Standard ☐ Priority ☐ Tropical disease Priority review voucher submitted
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐	
Part 3 Combination Product? ☐	☐ Drug/Biologic ☐ Drug/Device ☐ Biologic/Device
☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)

Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): 64,335	
PDUFA and Action Goal dates correct in tracking system? ***If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X YES ☐ NO
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established name to the supporting IND(s) if not already entered into tracking system.***	X YES ☐ NO
Are all classification codes/flags (e.g. orphan, OTC drug, pediatric data) entered into tracking system? ***If not, ask the document room staff to make the appropriate entries.***	X YES ☐ NO
Application Integrity Policy	
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ora/compliance_ref/aiplist.html*** **If yes**, explain: **If yes**, has OC/DMPQ been notified of the submission? **Comments**:	☐ YES X NO ☐ YES ☐ NO
User Fees	
Form 3397 (User Fee Cover Sheet) submitted	X YES ☐ NO
User Fee Status **Comments:**	X Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. It is expected that all 505(b) applications, whether 505(b)(1) or 505(b)(2), will require user fees unless otherwise waived or exempted (e.g., business waiver, orphan exemption).	
Exclusivity	
Does another product have orphan exclusivity for the same indication? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm*** **If yes**, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?	☐ YES X NO ☐ YES ☐ NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) **Comments:**	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** *Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.* **Comments:**	X YES # years requested: 5 ☐ NO
If the proposed product is a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***): Did the applicant (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b) request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***	**X** Not applicable ☐ YES ☐ NO
505(b)(2) (NDAs/NDA Efficacy Supplements only)	
	X Not applicable
1. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐ YES ☐ NO
2. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).	☐ YES ☐ NO
3. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))? *Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).*	☐ YES ☐ NO

4. Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm*** **If yes**, please list below:	☐ YES ☐ NO

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Format and Content	
Do not check mixed submission if the only electronic component is the content of labeling (COL). **Comments:**	☐ All paper (except for COL) X All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?	
If electronic submission: paper forms and certifications signed (non-CTD) or electronic forms and certifications signed (scanned or digital signature)(CTD)? ***Forms** include: 356h, patent information (3542a), financial disclosure (3454/3455), user fee cover sheet (3542a), and clinical trials (3674); **Certifications** include: debarment certification, patent certification(s), field copy certification, and pediatric certification.* **Comments:**	X YES ☐ NO
If electronic submission, does it follow the eCTD guidance? (*http://www.fda.gov/cder/guidance/7087rev.pdf*) **If not,** explain (e.g., waiver granted):	X YES ☐ NO

Form 356h: Is a signed form 356h included? ***If foreign applicant, both the applicant and the U.S. agent must sign the form.*** Are all establishments and their registration numbers listed on the form? **Comments:**	X YES ☐ NO X YES ☐ NO
Index: Does the submission contain an accurate comprehensive index? **Comments:**	X YES ☐ NO
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☐ legible ☐ English (or translated into English) ☐ pagination ☐ navigable hyperlinks (electronic submissions only) **If no**, explain:	X YES ☐ NO
Controlled substance/Product with abuse potential: Abuse Liability Assessment, including a proposal for scheduling, submitted? Consult sent to the Controlled Substance Staff? **Comments:**	X Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
BLAs/BLA efficacy supplements only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	 ☐ YES ☐ NO
Patent Information (NDAs/NDA efficacy supplements only)	
Patent information submitted on form FDA 3542a? **Comments:**	X YES ☐ NO
Debarment Certification	
Correctly worded Debarment Certification with authorized signature? ***If foreign applicant, both the applicant and the U.S. Agent must***	X YES ☐ NO

sign the certification. ***Note:*** *Debarment Certification should use wording in FD&C Act section 306(k)(l) i.e., "[Name of applicant] 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." Applicant may not use wording such as, "To the best of my knowledge..."* **Comments:**	
Field Copy Certification (NDAs/NDA efficacy supplements only)	
Field Copy Certification: that it is a true copy of the CMC technical section (***applies to paper submissions only***) ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐ Not Applicable (*electronic submission or no CMC technical section*) X YES ☐ NO
Financial Disclosure	
Financial Disclosure forms included with authorized signature? ***Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an Agent.*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.* **Comments:**	X YES ☐ NO
Pediatrics	
PREA ***Note:*** *NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.* Are the required pediatric assessment studies or a full waiver of pediatric studies included? **If no,** is a request for full waiver of pediatric studies OR a request for partial waiver/deferral and a pediatric plan included? • ***If no, request in 74-day letter.*** • **If yes,** does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) **Comments:**	☐ Not Applicable X YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO

BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, contact PMHS (pediatric exclusivity determination by the Pediatric Exclusivity Board is needed).*** **Comments:**	☐ YES X NO
Prescription Labeling	
Check all types of labeling submitted. **Comments:**	☐ **Not applicable** X Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use ☐ MedGuide X Carton labels X Immediate container labels ☐ Diluent ☐ Other (specify)
Is electronic Content of Labeling submitted in SPL format? ***If no, request in 74-day letter.*** **Comments:**	X YES ☐ NO
Package insert (PI) submitted in PLR format? **If no**, was a waiver or deferral requested before the application was received or in the submission? **If before**, what is the status of the request? ***If no, request in 74-day letter.*** **Comments:**	X YES ☐ NO ☐ YES ☐ NO
All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? **Comments:**	X YES ☐ NO
MedGuide or PPI (plus PI) consulted to OSE/DRISK? (*send WORD version if available*) **Comments:**	X Not Applicable ☐ YES ☐ NO
REMS consulted to OSE/DRISK? **Comments:**	X Not Applicable ☐ YES ☐ NO
Carton and immediate container labels, PI, PPI, and proprietary name (if any) sent to OSE/DMEDP? **Comments:**	☐ Not Applicable X YES ☐ NO

OTC Labeling	
Check all types of labeling submitted. **Comments:**	**X Not Applicable** ☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)
Is electronic content of labeling submitted? ***If no, request in 74-day letter.*** **Comments:**	☐ YES ☐ NO
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.*** **Comments:**	☐ YES ☐ NO
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.*** **Comments:**	☐ YES ☐ NO
Proprietary name, all labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEDP? **Comments:**	☐ YES ☐ NO
Meeting Minutes/SPA Agreements	
End-of Phase 2 meeting(s)? ***If yes, distribute minutes before filing meeting.*** **Comments:**	X YES Date(s): 12-6-05 ☐ NO
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? ***If yes, distribute minutes before filing meeting.*** **Comments:**	X YES Date(s): 6-6-07 ☐ NO
Any Special Protocol Assessment (SPA) agreements? ***If yes, distribute letter and/or relevant minutes before filing meeting.*** **Comments:**	☐ YES Date(s): X NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: July 9, 2008

NDA/BLA #: 22-308

PROPRIETARY/ESTABLISHED NAMES: OPTURA (besifloxacin hydrochloride ophthalmic suspension)

APPLICANT: Bausch & Lomb, Inc.

BACKGROUND: Besifloxacin HCl is a new chemical entity developed by Bausch& Lomb, Inc., for the treatment of bacterial conjunctivitis in adults and pediatric patients one year and older.

(Provide a brief background of the drug, (e.g., molecular entity is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Alison Rodgers	Y
	CPMS/TL:	Maureen Dillon-Parker	N
Cross-Discipline Team Leader (CDTL)	William Boyd		N
Clinical	Reviewer:	Martin Nevitt	Y
	TL:	William Boyd	N
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
OSE	Reviewer:	Carlos Menas-Grillasca	N
	TL:		

Clinical Microbiology (*for antimicrobial products*)	Reviewer:	Kerry Snow	Y
	TL:	Fred Marsik	N

Clinical Pharmacology	Reviewer:	Ryan Owen	N
	TL:	Chuck Bonapace	N
Biostatistics	Reviewer:	Yunfan Deng	Y
	TL:	Thamban Valappil	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Amy Ellis	Y
	TL:	Wendy Schmidt	N
Statistics, carcinogenicity	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Andy Yu	Y
	TL:	Linda Ng	Y
Facility (*for BLAs/BLA supplements*)	Reviewer:		
	TL:		
Microbiology, sterility (*for NDAs/NDA efficacy supplements*)	Reviewer:	John Metcalfe	Y
	TL:	Jim McVey	N
Bioresearch Monitoring (DSI)	Reviewer:	Jean Mulinde	Y
	TL:		
Other reviewers			

OTHER ATTENDEES: Lucious Lim, Lori Gorski, Jennifer Harris, Dave Roeder, Ed Cox, Wiley Chambers

505(b)(2) filing issues? **If yes,** list issues:	X Not Applicable ☐ YES ☐ NO
Per reviewers, are all parts in English or English translation? **If no**, explain:	X YES ☐ NO

Electronic Submission comments **List comments:**	☐ Not Applicable
CLINICAL **Comments:**	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	X YES ☐ NO
• Advisory Committee Meeting needed? **Comments:** ***If no, for an original NME or BLA application, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	X YES Date if known: TBD ☐ NO ☐ To be determined Reason:
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments:**	X Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments:**	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY	☐ Not Applicable X FILE ☐ REFUSE TO FILE

Comments:	☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES X NO
BIOSTATISTICS **Comments:**	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments:**	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments:**	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments:**	☐ Not Applicable X YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
• Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments:**	☐ Not Applicable X YES ☐ NO ☐ Not Applicable X YES ☐ NO
• Sterile product?	X YES ☐ NO

If yes, was Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**)	X YES ☐ NO
FACILITY (BLAs only) **Comments:**	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Office Director

GRMP Timeline Milestones: Mid-Cycle Meeting: 10-22-08; Reviews due: 1-31-09; PDUFA goal date: 4-2-09

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
X☐	The application, on its face, appears to be suitable for filing. ☐ No review issues have been identified for the 74-day letter. X Review issues have been identified for the 74-day letter. List (optional): (Items sent to sponsor via email on 7-11-08.) X Standard Review ☐ Priority Review

ACTIONS ITEMS

X	Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into tracking system.
☐	If RTF action, notify everybody who already received a consult request, OSE PM., and Product Quality PM. Cancel EER/TBP-EER.
☐	If filed and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
	If BLA or priority review NDA, send 60-day letter.
X	Send review issues/no review issues by day 74

☐	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

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

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

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

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

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

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

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

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

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

/s/

Alison Rodgers
7/15/2008 02:26:16 PM
CSO

Alison Rodgers
7/15/2008 02:28:29 PM
CSO

PMR/PMC Title:

A randomized, parallel arm, vehicle-controlled, clinical trial to evaluate the safety of Besivance (besifloxacin ophthalmic suspension) 0.6% when administered three times a day, four to twelve hours apart for 7 days.

PMR/PMC Schedule Milestones:

Final Protocol Submission:	October 2009
Trial Completion Date:	April 2012
Final Report Submission:	October 2012.

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

Unknown safety risk for patients who receive therapy of 7 days duration.

2. If required, characterize the **PMR**. Check all that apply and add text where indicated. ***If not a PMR, skip to*** 3.

- **Which regulation?**
  - ☐ Accelerated approval
  - ☐ Animal efficacy confirmatory studies
  - ☐ Pediatric requirement
  - ☒ FDAAA required safety study/clinical trial

- **Describe the particular review issue leading to the PMR**

Unknown safety risk for patients who receive therapy of 7-days duration.

- **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

An analysis of spontaneous postmarketing adverse events will not be sufficient to identify an unexpected serious risk of ophthalmic adverse events for patients who receive therapy of 7-days duration.

- **If the PMR is a FDAAA safety study/clinical trial, does it:**
  - ☐ Assess a known serious risk related to the use of the drug?
  - ☐ Assess signals of serious risk related to the use of the drug?
  - ☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - ☐ Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis

will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

N/A

4. If not required by regulation, characterize the review issue leading to this **PMC**

N/A

5. What type of study or clinical trial is required or agreed upon (describe)?

A randomized, parallel arm, vehicle-controlled, clinical trial to evaluate the safety of Besivance (besifloxacin ophthalmic suspension) 0.6% when administered three times a day, four to twelve hours apart for 7 days. The clinical trial must enroll at least 300 patients with signs and symptoms of bacterial conjunctivitis (ocular redness and discharge). Patients may be randomized in a 2:1 ratio, Besivance: control, for the objective of collecting safety data from the trial. Subjects should also be followed for clinical outcomes as this information can be important in the assessment of the safety data from the trial. Microbial cultures are required at baseline.

Required

- ☐ Pharmacoepidemiologic study (list risk to be evaluated)
- ☐ Registry studies
- ☒ Primary safety study or clinical trial (list risk to be evaluated)

  Adverse events associated with 7 day dosing.
- ☐ Subpopulation (list type)
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
- ☐ Nonclinical study (laboratory resistance, receptor affinity)
- ☐ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing studies
- ☐ Additional data or analysis required for a previously submitted or expected study (provide explanation)
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
- ☐ Immunogenicity as a marker of safety
- ☐ Other (provide explanation)

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup)
- ☐ Dose-response study performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)
- ☐ Other

6. Is the PMR/PMC clear and feasible?
   - ☒ Are the schedule milestones and objectives clear?
   - ☒ Has the applicant adequately justified the choice of schedule milestone dates?
   - ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

CDTL or PMR/PMC Development Coordinator:
This PMR/PMC has been reviewed for clarity and consistency, and is

necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]		
NDA # 22-308 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: BESIVANCE Established/Proper Name: besifloxacin hydrochloride ophthalmic suspension, 0.6% Dosage Form: Topical		Applicant: Bausch & Lomb Agent for Applicant (if applicable):
RPM: Alison Rodgers		Division: Anti-Infective and Ophthalmology Products

NDAs:	505(b)(2) Original NDAs and 505(b)(2) NDA supplements:
NDA Application Type: X 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)	Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)): Provide a brief explanation of how this product is different from the listed drug. ☐ If no listed drug, check here and explain: **Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.** ☐ No changes ☐ Updated Date of check: **If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.** **On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.**

❖ User Fee Goal Date Action Goal Date (if different)	4-2-09
❖ Actions	
• Proposed action	X AP ☐ TA ☐ AE ☐ NA ☐ CR
• Previous actions *(specify type and date for each action taken)*	X None
❖ Promotional Materials *(accelerated approvals only)* Note: If accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see guidance www.fda.gov/cder/guidance/2197dft.pdf). If not submitted, explain _____	☐ Received

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

Application[2] Characteristics	
Review priority: X Standard ☐ Priority Chemical classification (new NDAs only): 1 ☐ Fast Track ☐ Rolling Review ☐ Orphan drug designation ☐ Rx-to-OTC full switch ☐ Rx-to-OTC partial switch ☐ Direct-to-OTC NDAs: Subpart H ☐ Accelerated approval (21 CFR 314.510) ☐ Restricted distribution (21 CFR 314.520) Subpart I ☐ Approval based on animal studies BLAs: Subpart E ☐ Accelerated approval (21 CFR 601.41) ☐ Restricted distribution (21 CFR 601.42) Subpart H ☐ Approval based on animal studies ☐ Submitted in response to a PMR ☐ Submitted in response to a PMC Comments: _____	
❖ Date reviewed by PeRC *(required for approvals only)* If PeRC review not necessary, explain: _____	7-30-08
❖ BLAs only: *RMS-BLA Product Information Sheet for TBP* has been completed and forwarded to OBPS/DRM *(approvals only)*	☐ Yes, date
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	X Yes ☐ No
• Press Office notified of action (by OEP)	X Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None X HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

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

Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	X No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	X No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	X No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	X Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified

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

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

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

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

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

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

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

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

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

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

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

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

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

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[3]	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	X Included
Documentation of consent/non-consent by officers/employees	X Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Approval: 5-28-09
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	5-19-09
• Original applicant-proposed labeling	5-30-08
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Medication Guide/Patient Package Insert/Instructions for Use *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use X None

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

• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date at upper right of first page of each submission)*	
• Most-recent division proposal for (only if generated after latest applicant submission)	
• Most recent applicant-proposed labeling	5-19-09 (carton); 3-31-09 (container)
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☐ RPM ☐ DMEDP ☐ DRISK X DDMAC 1-26-09 ☐ CSS X Other reviews DMEPA 3-11-09
❖ Proprietary Name • Review(s) *(indicate date(s))* • Acceptability/non-acceptability letter(s) *(indicate date(s))*	 3-27-09; 9-23-08 4-2-09; 10-7-08
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)*	7-15-08
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	X Included
❖ Application Integrity Policy (AIP) Status and Related Documents www.fda.gov/ora/compliance_ref/aip_page.html	
• Applicant in on the AIP	☐ Yes X No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes X No ☐ Not an AP action
❖ Pediatric Page *(approvals only, must be reviewed by PERC before finalized)*	X Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	X Verified, statement is acceptable
❖ Postmarketing Requirement (PMR) Studies	X
• Outgoing communications *(if located elsewhere in package, state where located)*	Please see Approval Letter.
• Incoming submissions/communications	
❖ Postmarketing Commitment (PMC) Studies	X None

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

• Outgoing Agency request for postmarketing commitments *(if located elsewhere in package, state where located)*	
• Incoming submission documenting commitment	
❖ Outgoing communications *(letters (except previous action letters), emails, faxes, telecons)*	3-3-09; 02-18-09; 02-17-09; 02-10-09; 01-16-08; 01-13-09; 12-2-08; 10-21-08; 10-10-08 (2); 10-09-08; 09-16-08; 09-03-08; 07-31-08; 07-11-08; 06-27-08; 02-27-08; 02-04-08
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• PeRC *(indicate date; approvals only)*	☐ Not applicable 7-30-08
• Pre-Approval Safety Conference *(indicate date; approvals only)*	☐ Not applicable 3-2-09
• Regulatory Briefing *(indicate date)*	X No mtg
• Pre-NDA/BLA meeting *(indicate date)*	☐ No mtg 6-6-07
• EOP2 meeting *(indicate date)*	☐ No mtg 12-6-05
• Other (e.g., EOP2a, CMC pilot programs)	
❖ Advisory Committee Meeting(s)	☐ No AC meeting
• Date(s) of Meeting(s)	12-5-08
• 48-hour alert or minutes, if available	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☐ None 5-28-09
Division Director Summary Review *(indicate date for each review)*	☐ None 4-4-09
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 4-4-09
Clinical Information[5]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	Please see Cross-Discipline Team Leader Review dated 4-4-09
• Clinical review(s) *(indicate date for each review)*	4-2-09; 3-18-09; 3-4-09
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	X None
❖ Safety update review(s) *(indicate location/date if incorporated into another review)*	Please see page 46 of Clinical Review.
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	Please see page 6 of Clinical Review.
❖ Clinical reviews from other clinical areas/divisions/Centers *(indicate date of each review)*	X None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	X Not needed

[5] Filing reviews should be filed with the discipline reviews.

❖ Risk Management • Review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)* • REMS Memo *(indicate date)* • REMS Document and Supporting Statement *(indicate date(s) of submission(s))*	X None
❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested 5-29-09; 5-29-09; 2-23-09; 2-23-09; 2-20-09; 2-18-09 2-13-09 (2)
Clinical Microbiology ☐ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	X None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None 3-25-09; 2-11-09; 7-9-08
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	X None
Statistical Team Leader Review(s) *(indicate date for each review)*	X None
Statistical Review(s) *(indicate date for each review)*	☐ None 3-30-09; 2-5-09
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	X None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	X None
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 1-29-09; 8-20-08
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	X None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	X None
• Supervisory Review(s) *(indicate date for each review)*	☐ None 2-27-09
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 2-10-09
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	X None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	X No carc
❖ ECAC/CAC report/memo of meeting	X None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	X None requested
CMC/Quality ☐ None	
❖ CMC/Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☐ None 2-20-09
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	X None
• CMC/product quality review(s) *(indicate date for each review)*	☐ None 2-17-09; 2-9-09; 1-29-09; 10-1-08
• BLAs only: Facility information review(s) *(indicate dates)*	☐ None

❖ Microbiology Reviews • NDAs: Microbiology reviews (sterility & pyrogenicity) *(indicate date of each review)* • BLAs: Sterility assurance, product quality microbiology *(indicate date of each review)*	1-7-09; 8-19-08 ☐ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	X None
❖ Environmental Assessment (check one) (original and supplemental applications)	
X Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	See page 155 of CMC/Quality Review dated 1-29-09.
☐ Review & FONSI *(indicate date of review)*	N/A
☐ Review & Environmental Impact Statement *(indicate date of each review)*	N/A
❖ NDAs: Methods Validation	**X** Completed ☐ Requested ☐ Not yet requested ☐ Not needed
❖ Facilities Review/Inspection	
• NDAs: Facilities inspections (include EER printout) *(date completed must be within 2 years of action date)*	Date completed: 2-11-09 [redacted] b(4) 1-26-09(All other facilities) **X** Acceptable ☐ Withhold recommendation
• BLAs: o TBP-EER o Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) *(date completed must be within 60 days prior to AP)*	Date completed: ☐ Acceptable ☐ Withhold recommendation Date completed: ☐ Requested ☐ Accepted ☐ Hold