

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**202872Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

**PATENT INFORMATION SUBMITTED WITH THE FILING  
OF AN NDA, AMENDMENT, OR SUPPLEMENT**

**For Each Patent That Claims a Drug Substance  
(Active Ingredient), Drug Product (Formulation and Composition)  
and/or Method of Use**

NDA NUMBER

202872

NAME OF APPLICANT/NDA HOLDER

Bausch and Lomb, Incorporated

*The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.*

TRADE NAME (OR PROPOSED TRADE NAME)

(b) (4)  
loteprednol etabonate ophthalmic gel, 0.5%

ACTIVE INGREDIENT(S)

loteprednol etabonate

STRENGTH(S)

0.5%

DOSAGE FORM

gel

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).

Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

**For hand-written or typewriter versions (only) of this report:** If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

**FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.**

**For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.**

**1. GENERAL**

a. United States Patent Number

5,800,807

b. Issue Date of Patent

September 1, 1998

c. Expiration Date of Patent

January 29, 2017

d. Name of Patent Owner

Bausch & Lomb Incorporated

Address (of Patent Owner)

One Bausch & Lomb Place

City/State

Rochester, NY

ZIP Code

14604

FAX Number (if available)

Telephone Number

(585) 338-8071

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

City/State

ZIP Code

Telephone Number

FAX Number (if available)

E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

**For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.**

**2. Drug Substance (Active Ingredient)**

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?  Yes  No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?  Yes  No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).  Yes  No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)  Yes  No

2.6 Does the patent claim only an intermediate?  Yes  No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**3. Drug Product (Composition/Formulation)**

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?  Yes  No

3.2 Does the patent claim only an intermediate?  Yes  No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**4. Method of Use**

**Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:**

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

4.2 Patent Claim Number(s) (as listed in the patent) Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.

Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)  
 (b) (4) is a topical gel and is indicated for the treatment of inflammation and pain following ocular surgery.

(b) (4)

**5. No Relevant Patents**

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.

Yes

**6. Declaration Certification**

**6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.**

**Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.**

**6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)**

Date Signed

Toan P. Vo

October 17, 2011

**NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).**

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Toan P. Vo, Ph.D.

Address

Bausch + Lomb Incorporated  
One Bausch + Lomb Place

City/State

Rochester, NY

ZIP Code

14604

Telephone Number

(585) 338-8071

FAX Number (if available)

(585) 338-8706

E-Mail Address (if available)

toan.p.vo@bausch.com

The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services  
Food and Drug Administration  
Office of Chief Information Officer  
1350 Piccard Drive, Room 400  
Rockville, MD 20850

*An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.*

**INFORMATION AND INSTRUCTIONS FOR FORM 3542a**  
**PATENT INFORMATION SUBMITTED WITH THE FILING**  
**OF AN NDA, AMENDMENT OR SUPPLEMENT**

**General Information**

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplement approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. Sending an additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of April 2007) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: <http://www.fda.gov/opacom/morechoices/fdaforms/fdaforms.html>.

**First Section**

Complete all items in this section.

**1. General Section**

Complete all items in this section with reference to the patent itself.

- 1c) Include patent expiration date, including any Hatch-Waxman patent extension already **granted**. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.
- 1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

- 1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

**2. Drug Substance (Active Ingredient)**

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.
- 2.7) Answer this question only if the patent is a product-by-process patent.

**3. Drug Product (Composition/Formulation)**

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

- 3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

**4. Method of Use**

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement (pending method of use).

- 4.2) For each pending method of use claimed by the patent, identify by number the claim(s) in the patent that claim the pending use of the drug. An applicant may list together multiple patent claim numbers and information for each pending method of use, if applicable. However, each pending method of use must be separately listed within this section of the form.
- 4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

**5. No Relevant Patents**

Complete this section only if applicable.

**6. Declaration Certification**

Complete all items in this section.

- 6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

**PATENT INFORMATION SUBMITTED WITH THE FILING  
OF AN NDA, AMENDMENT, OR SUPPLEMENT**

*For Each Patent That Claims a Drug Substance  
(Active Ingredient), Drug Product (Formulation and Composition)  
and/or Method of Use*

NDA NUMBER

202872

NAME OF APPLICANT/NDA HOLDER

Bausch and Lomb, Incorporated

*The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.*

TRADE NAME (OR PROPOSED TRADE NAME)

<sup>(b) (4)</sup>  
(loteprednol etabonate ophthalmic gel, 0.5%)

ACTIVE INGREDIENT(S)

loteprednol etabonate

STRENGTH(S)

0.5%

DOSAGE FORM

gel

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

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**For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.**

**1. GENERAL**

a. United States Patent Number

4,996,335

b. Issue Date of Patent

February 26, 1991

c. Expiration Date of Patent

March 9, 2012

d. Name of Patent Owner

Nicholas Bodor, Ph.D., D.Sc.

Address (of Patent Owner)

10225 Collins Avenue, #1002-1004

City/State

Bal Harbour, FL

ZIP Code

33154

FAX Number (if available)

Telephone Number

(305) 868-8250

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

City/State

ZIP Code

Telephone Number

FAX Number (if available)

E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

**For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.**

**2. Drug Substance (Active Ingredient)**

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?  Yes  No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?  Yes  No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).  Yes  No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)  Yes  No

2.6 Does the patent claim only an intermediate?  Yes  No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**3. Drug Product (Composition/Formulation)**

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?  Yes  No

3.2 Does the patent claim only an intermediate?  Yes  No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**4. Method of Use**

**Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:**

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

4.2 Patent Claim Number(s) (as listed in the patent) 89, 90 Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the proposed labeling.) (b) (4) is a topical gel and is indicated for the treatment of inflammation and pain following ocular surgery. (b) (4)

**5. No Relevant Patents**

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.  Yes

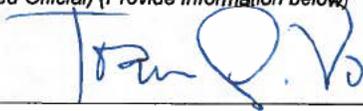
**6. Declaration Certification**

**6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.**

**Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.**

**6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)**

Date Signed



October 24, 2011

**NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).**

**Check applicable box and provide information below.**

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Toan P. Vo, Ph.D.

Address

Bausch + Lomb Incorporated  
One Bausch + Lomb Place

City/State

Rochester, NY

ZIP Code

14604

Telephone Number

(585) 338-8071

FAX Number (if available)

(585) 338-8706

E-Mail Address (if available)

toan.p.vo@bausch.com

The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services  
Food and Drug Administration  
Office of Chief Information Officer  
1350 Piccard Drive, Room 400  
Rockville, MD 20850

*An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.*

**INFORMATION AND INSTRUCTIONS FOR FORM 3542a**  
**PATENT INFORMATION SUBMITTED WITH THE FILING**  
**OF AN NDA, AMENDMENT OR SUPPLEMENT**

**General Information**

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplement approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. Sending an additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of April 2007) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: <http://www.fda.gov/opacom/morechoices/fdaforms/fdaforms.html>.

**First Section**

Complete all items in this section.

**1. General Section**

Complete all items in this section with reference to the patent itself.

- 1c) Include patent expiration date, including any Hatch-Waxman patent extension already **granted**. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.
- 1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

- 1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

**2. Drug Substance (Active Ingredient)**

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.
- 2.7) Answer this question only if the patent is a product-by-process patent.

**3. Drug Product (Composition/Formulation)**

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

- 3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

**4. Method of Use**

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement (pending method of use).

- 4.2) For each pending method of use claimed by the patent, identify by number the claim(s) in the patent that claim the pending use of the drug. An applicant may list together multiple patent claim numbers and information for each pending method of use, if applicable. However, each pending method of use must be separately listed within this section of the form.
- 4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

**5. No Relevant Patents**

Complete this section only if applicable.

**6. Declaration Certification**

Complete all items in this section.

- 6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

## EXCLUSIVITY SUMMARY

NDA # 202872

SUPPL #

HFD #

Trade Name Lotemax

Generic Name loteprednol etabonate ophthalmic gel, 0.5%

Applicant Name Bausch and Lomb

Approval Date, If Known September 29, 2012

### 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?

3 years

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?

No

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# 20-583 Lotemax (loteprednol etabonate ophthalmic suspension, 0.5%)  
NDA# 20-803 Alrex (loteprednol etabonate ophthalmic suspension, 0.2%)  
NDA# 200-738 Lotemax (loteprednol etabonate ophthalmic ointment, 0.5%)

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# 50-804 Zylet (loteprednol etabonate 0.5% and tobramycin 0.3% ophthalmic suspension

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:

Study #576: "Prospective, Multi-Center, Randomized, Double-masked, Parallel-Group, Clinical Safety and Efficacy Evaluation of Loteprednol Etabonate Ophthalmic Gel, 0.5% versus Vehicle for the Treatment of Inflammation and Pain following Cataract Surgery"

Study #577: "Prospective, Multi-Center, Randomized, Double-masked, Parallel-Group, Clinical Safety and Efficacy Evaluation of Loteprednol Etabonate Ophthalmic Gel, 0.5% versus Vehicle for the Treatment of Inflammation and Pain following Cataract Surgery"

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: Study 576 YES  NO

Investigation #2: Study 577 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: Study 576 YES  NO

Investigation #2: Study 577 YES  NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1: Study 576

Investigation #2: Study 577

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 Study 576 !  
IND # 102654 YES  ! NO   
! Explain:

Investigation #2  
IND # 102654 YES  ! NO   
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1  
!  
!  
YES  ! NO   
Explain: ! Explain:

Investigation #2  
!  
!  
YES  ! NO   
Explain: ! Explain:

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

YES  NO

If yes, explain:

=====

Name of person completing form: June Germain  
Title: Regulatory Project Manager (DTOP)  
Date: 11-21-12

Name of Office/Division Director signing form: Wiley A Chambers

Title: Deputy Director (DTOP)

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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/s/  
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JUNE GERMAIN  
11/26/2012

WILEY A CHAMBERS  
11/27/2012

## Germain, June

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**From:** Suggs, Courtney  
**Sent:** Wednesday, July 25, 2012 11:30 AM  
**To:** Germain, June  
**Cc:** Yao, Lynne P; Addy, Rosemary; Greeley, George; Lee, Catherine S.; Albrecht, Renata  
**Subject:** NDA 202-879 Loteprednol Etabonate

**Follow Up Flag:** Follow up  
**Flag Status:** Red

**Attachments:** 1\_Pediatric\_Record.pdf

Hi June,

The email serves as confirmation of the review for loteprednol etabonate ophthalmic gel conducted by the PeRC PREA Subcommittee on July 18, 2012.

Loteprednol etabonate was studied for the treatment of postoperative inflammation following ocular surgery. The Division presented a full deferral in pediatric patients from birth to  $\frac{6}{4}$  years of age because adult studies are completed and ready for approval.

The PeRC agreed with the Division to grant a full deferral in pediatric patients because adult studies are completed and the product is ready for approval in adults.

*If the Division intends to issue a second WR, the PeRC recommends:*

- *Enrolling at least 60 patients ages birth to 3 years to get sufficient safety data to detect an adverse event rate of 5% or greater.*
- *Enrolling patients up to 11 years of age to have a patient population large enough to demonstrate equivalence to PredForte.*
- *Extrapolating safety and efficacy data from patients ages birth to 11 years and from data of previously approved loteprednol products to support labeling in patients 12 to 16 years of age.*
- *The Division should Anticipate a discussion at PeRC of what other indications to include in the WR.*

The pediatric record is attached for loteprednol etabonate.



1\_Pediatric\_Record  
.pdf (60 KB)...

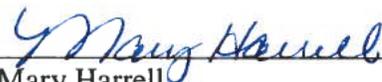
**Courtney M. Suggs, Pharm.D., MPH**

LCDR, USPHS  
Regulatory Project Manager  
Pediatric and Maternal Health Staff  
Office of New Drugs, Immediate Office  
Center for Drug Evaluation and Research  
US Food and Drug Administration  
10903 New Hampshire Ave.  
Bldg 22, Room 6471  
Silver Spring, MD 20993  
Phone: (301) 796-2096  
Email: courtney.suggs@fda.hhs.gov

2 Page(s) has been Withheld in Full as b5 immediately following this page

### 1.3.3 Debarment Certification

Bausch & Lomb 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.

  
\_\_\_\_\_  
Mary Harrell  
Manager - Brand  
Global Pharmaceutical Regulatory Affairs  
Bausch & Lomb, Incorporated

10/20/2011  
Date



NDA 202872

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Bausch & Lomb, Incorporated  
7 Giralda Farms, Suite 1001  
Madison, NJ 07940

ATTENTION: Mary Harrell  
Manager, Global Pharmaceutical Regulatory Affairs

Dear Ms. Harrell:

Please refer to your New Drug Application (NDA) dated and received November 29, 2012, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Loteprednol Etabonate Ophthalmic Gel, 0.5%.

We also refer to your correspondence, dated and received September 21, 2012, requesting review of your proposed proprietary name, Lotemax. We have completed our review of the proposed proprietary name, Lotemax and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your September 21, 2012, 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, contact Karen Townsend, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5413. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, June Germain at (301) 796-4024.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, RPh

Director

Division of Medication Error Prevention and Analysis

Office of Medication Error Prevention and Risk Management

Office of Surveillance and Epidemiology

Center for Drug Evaluation and Research

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/s/  
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CAROL A HOLQUIST  
09/25/2012



NDA 202872

## CONFIRMATION OF ISSUES DISCUSSED

Bausch & Lomb, Inc.  
Attention: Mary Harrell  
Manager, Brand  
7 Giralda Farms, Suite 1001  
Madison, New Jersey 07940

Dear Ms. Harrell:

Please refer to your New Drug Application (NDA) for loteprednol etabonate ophthalmic gel, 0.5%.

We also refer to your email request dated August 3, 2012, for a Chemistry, Manufacturing and Controls (CMC) teleconference, which states, "We are seeking advice on the impact to the review of an alternative proposal for the viscosity specification as mentioned in Comment #2 of the Information Request dated July 31, 2012. Specifically, we would like to provide a small amount of updated stability data (5 time points) for lots currently filed in the NDA to support an alternate proposal for the viscosity specification without impact to the review timeline (PDUFA goal date)."

In a CMC teleconference on August 6, 2012, the following issues were discussed between Bausch & Lomb, Inc. and the Office of New Drug Quality Assessment:

1. The Agency had proposed a viscosity specification of (b) (4) in Comment #2 of the Information Request letter dated July 31, 2012.
2. Bausch & Lomb counter-proposed a viscosity specification of (b) (4) with provision of data from 5 additional time points to support the specification.
3. FDA expressed concern that the highest value for viscosity observed during stability was (b) (4). In addition, no data has been submitted to date regarding thixotropic evaluation at (b) (4) and the range evaluated was (b) (4).
4. Bausch & Lomb asked if FDA requires a viscosity of (b) (4) for gel designation. FDA asked if the product does not retain gel characteristics at (b) (4) Bausch & Lomb responded that this was not an issue.
5. FDA emphasized that data would need to be submitted to justify the proposed upper viscosity limit of (b) (4).
6. FDA asked if the request for (b) (4) is related to the shelf-life. Bausch & Lomb replied no, they intend to keep the current shelf-life.
7. FDA requested that data for all test attributes at the new 5 time points be submitted, not just those for viscosity, as Bausch & Lomb had proposed.

8. Bausch & Lomb asked if that would affect the review timeline. If it would, Bausch & Lomb implied that they may adopt the Agency's proposal (item 1 above). FDA said that they cannot determine whether or not the timeline would be affected without reviewing the data.

In addition, we have the following post-meeting comment: we note that for the 14 day in-use study provided in the Pharmaceutical Development section, the product viscosity was (b) (4) [redacted]. No in-use data has been provided to support (b) (4) [redacted].

If you have any questions, call Althea Cuff, Regulatory Project Manager, at (301) 796-4061.

Sincerely,

*{See appended electronic signature page}*

Rapti D. Madurawe, Ph.D.  
Branch Chief, Branch V  
Division of New Drug Quality Assessment II  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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/s/  
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RAPTI D MADURawe  
08/07/2012



NDA 202-872

**INFORMATION REQUEST**

Bausch & Lomb, Inc.  
Attention: Mary Harrell  
Manager, Brand  
7 Giralda Farms, Suite 1001  
Madison, New Jersey 07940

Dear Ms. Harrell:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for loteprednol etabonate ophthalmic gel, 0.5%.

We are reviewing the Chemistry, Manufacturing and Control section of your submission and have the following comments and information requests. We request a prompt written response by August 6, 2012, in order to continue our evaluation of your NDA.

1. We noted that some acceptance criteria listed in the drug substance stability data (3.2.S.7.3) are different to those in the proposed drug substance specification. Please confirm that stability studies will be monitored and reported according to the proposed sterile drug substance specification.
2. We acknowledge that the acceptance criterion for the drug product viscosity will be revised upon review of the stability data from the process validation lots. In the interim, based on the review of the submitted data we recommend that the acceptance criterion be revised to (b) (4).
3. We are currently evaluating the designation of the dosage form. Please provide a sample of loteprednol etabonate ophthalmic suspension 0.5% as a dosage form comparator.

If you have any questions, call Althea Cuff, Regulatory Health Project Manager, at (301) 796-4061.

Sincerely,

*{See appended electronic signature page}*

Rapti D. Madurawe, Ph.D.  
Branch Chief, Branch V  
Division of New Drug Quality Assessment II  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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/s/  
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RAPTI D MADURawe  
07/31/2012



NDA 202-872

**INFORMATION REQUEST**

Bausch & Lomb, Inc.  
Attention: Mary Harrell  
Manager, Brand  
7 Giralda Farms, Suite 1001  
Madison, New Jersey 07940

Dear Ms. Harrell:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for loteprednol etabonate ophthalmic gel, 0.5%.

We are reviewing the Chemistry, Manufacturing and Control section of your submission and have the following comments and information requests. We request a prompt written response by June 15, 2012, in order to continue our evaluation of your NDA.

1. Provide the following information on the (b) (4) used for packaging the drug substance.
  - a. A detailed description of the (b) (4) (such as dimensions, relevant material information, supplier name, etc.)
  - b. A statement or a reference to the appropriate indirect food additive regulation to establish the safety of the materials of construction.
  - c. Indicate if the (b) (4). If they do, provide information to show that these (b) (4) conform to the relevant 21 CFR 178.3130 regulations.
  - d. A certificate of analysis for the (b) (4)
2. Provide the following information on the drug substance
  - a. Chromatograms for Lot#100506211B before and after sterilization. Any new impurities obtained after sterilization may need identification or qualification information depending on the levels observed.
  - b. The level for the largest single unknown impurity for Lot #100506211B is (b) (4) which is higher than the proposed acceptance criteria of (b) (4) and above the identification threshold according to ICH Q3A. Identify this impurity.
3. Provide batch release data for all drug product lots used in clinical studies, including lot 247231.

4. It is stated that the (b) (4) overage has been verified to be appropriate for manufacturing the drug product at the (b) (4) scale. Please justify what the (b) (4) overage accounts for. Use of overages (b) (4) is not recommended.
5. Figure 3.2.P.2.2-8 shows weight of each dispensed dose. To assure suspension uniformity of the drug during in-use, provide the measured values of loteprednol etabonate in each dispensed dose.
6. The leachable, (b) (4) is present in the drug product. Include a limit for (b) (4) in the drug product specification.
7. Based on the stability data, the following acceptance criteria are recommended for drug product shelf-life:
  - a. NMT (b) (4)
  - b. NMT (b) (4)
8. The observed viscosity range using viscometer #2 (b) (4) is (b) (4). (b) (4) The acceptance criterion for the drug product viscosity test, (b) (4), is (b) (4). Please (b) (4) the specification.
9. Provide data to support that thixotropic behavior is maintained over the high and low limits of the viscosity range. Discuss what attributes affect thixotropic behavior.
10. It is stated in 3.2.P.8.2 that “*The first three commercial scale lots of drug product (process validation lots) will be placed on stability in accordance with the stability protocol through the proposed expiration period and stored in the upright and horizontal orientations. Thereafter, one lot of each fill size manufactured will be placed on stability annually, stored in the upright orientation*”. We recommend the horizontal orientation be selected, instead of the upright orientation. Revise the statement accordingly.
11. Discuss the control procedures to limit the level of (b) (4) in the sterilized container closure system and indicate the specification limit.
12. Please provide a drug product sample for each of the fill sizes

If you have any questions, call Althea Cuff, Regulatory Health Project Manager, at (301) 796-4061.

Sincerely,

*{See appended electronic signature page}*

Rapti D. Madurawe, Ph.D.  
Branch Chief, Branch V  
Division of New Drug Quality Assessment II  
Office of New Drug Quality Assessment

Center for Drug Evaluation and Research

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/s/  
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RAPTI D MADURawe  
05/17/2012

NDA 202872  
loteprednol etabonate ophthalmic gel, 0.5%  
Bausch and Lomb, Inc  
Information Request

**INFORMATION REQUEST**

Dear Ms. Harrell,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for loteprednol etabonate ophthalmic gel, 0.5%.

We are reviewing the product quality section of your submission and have the following information request. We request a response by March 31, 2012 in order to continue our evaluation of your NDA.

Drug substance:

- 1) Provide the results of the most recent quarterly audit of the (b) (4) of the drug substance.
- 2) The specifications for bioburden and sterility are footnoted as "Required for retest interval". Provide the retest interval.
- 3) Provide a description of the bioburden test method.
- 4) Regarding the USP <71> sterility test, both (b) (4) and (b) (4) methods were tested for suitability. The (b) (4) method described (b) (4)

Drug product:

- 1) Regarding the (b) (4) (b) (4)

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/s/  
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JUNE GERMAIN  
05/16/2012



NDA 202872

**FILING COMMUNICATION**

Bausch & Lomb, Inc.  
Attention: Mary Harrell  
Manager, Brand  
7 Giralda Farms, Suite 1001  
Madison, New Jersey 07940

Dear Ms. Harrell:

Please refer to your New Drug Application (NDA) dated and received November 29, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for loteprednol etabonate ophthalmic gel, 0.5%.

This application proposes the use of loteprednol etabonate ophthalmic gel for the treatment of inflammation and pain following ocular surgery.

(b) (4)

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application was considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is September 29, 2012.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by September 1, 2012.

## **PROMOTIONAL MATERIAL**

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

## **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We note that you have not submitted a pediatric plan as required by Federal Food, Drug, and Cosmetic Act (FDCA), section 505 (b) [355c], and we also make reference to the January 27, 2012 telephone conversation where we discussed with you this requirement. Within 14 days of the date of this letter, please submit a pediatric drug development plan covering the full pediatric age range. A pediatric drug development plan must specifically address the indication proposed in this application.

If you have any questions, call Ms. June Germain, Senior Regulatory Project Manager, at (301) 796-4024.

Sincerely,

*{See appended electronic signature page}*

Renata Albrecht, MD  
Director  
Division of Transplant and Ophthalmology Products  
Office of Antimicrobial Products  
Office of New Drugs  
Center for Drug Evaluation and Research

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/s/  
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RENATA ALBRECHT  
02/07/2012



NDA 202872

**PROPRIETARY NAME REQUEST  
UNACCEPTABLE**

Bausch & Lomb, Incorporated  
7 Giralda Farms, Suite 1001  
Madison, New Jersey 07940

ATTENTION: Mary Harrell  
Manager, Global Pharma Regulatory Affairs

Dear Ms. Harrell:

Please refer to New Drug Application (NDA) dated November 29, 2011, received November 29, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Loteprednol Etabonate Ophthalmic Gel, 0.5%.

We also refer to your November 21, 2011, correspondence, received November 29, 2011, requesting review of your proposed proprietary name, (b) (4). We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable for the following reason:

(b) (4)

Please note that the Federal Food Drug and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made, whether through a proposed proprietary name or otherwise; this includes suggestions that a drug is better, more effective, useful in a broader range of conditions or patients, safer, has fewer, or lower incidence of, or less serious side effects or contraindications than has been demonstrated by substantial evidence or substantial clinical experience. [21 U.S.C. 321(n); see also 21 U.S.C. 352(a) & (n); 21 CFR 202.1(e)(5)(i);(e)(6)(i)].

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> and “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”.)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Karen Townsend, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5413. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, June Germain, at (301) 796-4024.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, RPh

Director

Division of Medication Error Prevention and Analysis

Office of Medication Error Prevention and Risk Management

Office of Surveillance and Epidemiology

Center for Drug Evaluation and Research

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/s/  
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CAROL A HOLQUIST  
01/31/2012

NDA 202872  
Loteprednol etabonate ophthalmic gel, 0.5%  
Bausch and Lomb, Inc  
Information Request

**INFORMATION REQUEST**

Dear Ms. Harrell,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for loteprednol etabonate ophthalmic gel, 0.5%.

We are reviewing the clinical section of your submission and have the following information request. We request a response by February 3, 2012 in order to continue our evaluation of your NDA.

Please provide a revised List and Description of Investigators for Studies #576 and #577 (found in appendix 16.1.4 in each study report) and include the number of subjects enrolled by each site for each treatment arm.

Please call me if you have further questions.

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/s/  
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JUNE GERMAIN  
01/24/2012

## MEMORANDUM OF MEETING MINUTES

**MEETING DATE:** January 17, 2012  
**TIME:** 12:30 To 1:00 PM  
**LOCATION:** Teleconference  
**APPLICATION:** NDA 202872  
**DRUG NAME:** loteprednol etabonate ophthalmic gel, 0.5%  
**TYPE OF MEETING:** filing issues meeting

**MEETING CHAIR:** Wiley Chambers, MD

**MEETING RECORDER:** June Germain, RPM

### FDA DIVISION OF TRANSPLANT AND OPHTHALMOLOGY ATTENDEES:

Renata Albrecht, MD	Director
Wiley Chamber, MD	Deputy Director
William Boyd, MD	Medical Team Leader
Lucious Lim, MD	Medical Reviewer
Judit Milstein	Chief Project Management Staff
June Germain, M.S	Senior Regulatory Project Manager

### EXTERNAL CONSTITUENT ATTENDEES:

Art Ciociola	VP, Global Regulatory Affairs
Isabelle Lefebvre	Director, Global Regulatory Affairs
Mary Harrell	Manager, Global Regulatory Affairs
Tuyen Ong	Executive Director, Global Clinical; Development
Raphaele Siou-Mermet	Manager, Pharmaceutical Clinical Science
Kathleen Krenzer	Principal Scientist, Nonclinical Safety
Kristy Quinzi	Manager, Program Management

### BACKGROUND:

On November 29, 2011 Bausch and Lomb (B&L) submitted a New Drug Application (NDA) for (b) (4) (loteprednol etabonate) ophthalmic gel, 0.5% for (b) (4) indication, the treatment of inflammation and pain following ocular surgery (b) (4)

On January 13, 12 the Division (DTOP) requested a teleconference with B&L to discuss filing issues.

### MEETING OBJECTIVES:

**DISCUSSION POINTS:**

The Division stated that the NDA was received with the (b) (4) noted that upon initial review 2 clinical trials to support the indication treatment of inflammation and pain following ocular surger (b) (4)

The Division asked the applicant to identify where in the application this was located. The Division noted that there were three options:

**ACTION ITEMS:**

B& L to submit a revise labeling (b) (4)

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/s/  
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JUNE GERMAIN  
08/08/2012



NDA 202,872

**NDA ACKNOWLEDGMENT**

Bausch & Lomb, Inc.  
Attention: Mary Harrell  
Manager, Global Pharmaceutical Regulatory Affairs  
7 Giralda Farms, Suite 1001  
Madison, New Jersey 07940

Dear Ms. Harrell:

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: (b) (4) (loteprednol etabonate) ophthalmic gel, 0.5%

Date of Application: November 29, 2011

Date of Receipt: November 29, 2011

Our Reference Number: NDA 202,872

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 January 28, 2012, 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/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. 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.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

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 Transplant and Ophthalmology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have any questions, call me, Senior Regulatory Project Manager, at (301) 796-4024.

Sincerely,

*{See appended electronic signature page}*

June Germain, M.S.  
Senior Regulatory Project Manager  
Division of Transplant and Ophthalmology  
Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

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/s/  
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JUNE GERMAIN

12/06/2011

acknowledge NDA submission



NDA 202872

**MEETING MINUTES**

Bausch & Lomb, Inc.  
Attn: Fang Li, Ph.D., RAC  
Associate Director, Brand Global Regulatory Affairs  
7 Giralda Farms, Suite 1001  
Madison, NJ 07940

Dear Dr. Li:

Please refer to the Type B meeting between representatives of your firm and FDA on April 29, 2011. The purpose of the meeting was to discuss the non-clinical, clinical and chemistry programs for loteprednol etabonate ophthalmic gel, 0.5% proposed for treatment of inflammation and pain following ocular surgery.

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 Raphael R. Rodriguez, Regulatory Project Manager, at (301) 796-0798.

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

Enclosure

## MEMORANDUM OF MEETING MINUTES

**Meeting Type:** Type B  
**Meeting Category:** Pre-NDA meeting

**Meeting Date and Time:** April 29, 2011, (9:00 – 10:00 EST)  
**Meeting Location:** White Oak, BLDG #22, RM #1311

**Application Number:** NDA 202872

**Product Name:** Loteprednol Etabonate Ophthalmic Gel 0.5%

**Proposed Indication:** Treatment of post operative inflammation and pain following ocular surgery.

**Sponsor/Applicant Name:** Bausch & Lomb, Inc.

**Meeting Chair:** Wiley A. Chambers, M.D.  
**Meeting Recorder:** Raphael R. Rodriguez

**FDA Attendees:** Wiley Chambers, William Boyd, Martin Nevitt, Rhea Lloyd, Conrad Chen, Wendy Schmidt, Linda Ng, Irem Rima, Yan Wang, Raphael Rodriguez

**Bausch & Lomb Attendees:** Fang Li, Arthur Ciociola, Kirk Bateman, Stephen Davio, Kathleen Krenzer, Baldo Sforzolini, Tuyen Ong, Mary E Harrell

## 1. BACKGROUND

The purpose of this meeting is to discuss the non-clinical, clinical and chemistry programs for loteprednol etabonate ophthalmic gel, 0.5% proposed for treatment of inflammation and pain following ocular surgery

## 2. DISCUSSION

### **Nonclinical**

*Question #1:* Does the Agency agree that the nonclinical development package described in the meeting package is adequate to support the NDA submission and review for loteprednol etabonate ophthalmic gel, 0.5%?

**RESPONSE:** Agree.

*Question #2* Does the Agency agree that based on the well-established safety profile of loteprednol etabonate there is no need to conduct a carcinogenicity study and a waiver will be granted?

**RESPONSE:** Waivers for carcinogenicity studies were granted previously for other LE products (Lotemax, Alrex, and Zylet; NDAs 20-583, 20-803, and 50-804, respectively). The waiver is also recommended for this NDA.

### **Clinical**

*Question #3* Does the Agency agree that the clinical program described in this meeting package adequately supports the Agency evaluation of efficacy and safety for the proposed indication?

**RESPONSE:** The clinical program appears adequate to support filing for the proposed indication although final determination can only be made after review of the NDA submission.

*Question #4* Does the Agency agree the NDA will be accepted for filing with the proposed plan for requesting a deferral for pediatric study required by PREA, provided that we meet other requirements for the NDA?

**RESPONSE:** The proposal to request a deferral for a pediatric study is acceptable. .

### **Chemistry**

*Question #5* Does the Agency agree that:

a) Submitting only (b) (4) data collected on all three lots at the 30°C/35%RH storage condition as described in Table 1 would be sufficient to support a claim of "Store upright between 15°– (b) (4) (59°– (b) (4))" in labeling?

- b) Submitting the data from a single lot stored horizontally for stability testing is adequate for the drug product?
- c) Submitting the data from a single lot for the physician sample is adequate to support the labeling for the physician sample?

**RESPONSE:**

- a. If (b) (4) containers are selected for the commercial product, at least one lot of each container configuration at both highest and lowest fill size is needed at the proposed (b) (4) RH through expiry.
- b. Similar to question 5 a, at least one lot of each container configuration at both highest and lowest fill size is needed for the horizontal orientation.
- c. One lot under appropriate storage conditions/orientations is adequate, if there is only one configuration for physician sample.

Data for all stability tests attributes and both orientations need to be provided. In addition, please reference ICH Q1A (R2) and Q1B, Q1D, and Q1E for stability studies.

*Question #6* Does the Agency agree that the stability program, described in Table 2, adequately meets the filing requirements for a New Drug Application?

**RESPONSE:** The stability program seems to satisfy the filing requirements for an NDA. However, the adequacy will be evaluated during NDA review.

*Question #7* Does the proposed plan adequately support Agency review of the stability data to gain approval of a 24-month shelf life during NDA review?

**RESPONSE:** A 24-month shelf life is not likely to be granted based on 12 month stability data. Approval of the proposed shelf-life will depend on the quantity and quality of the data.

*Question #8* Does the Agency agree that the Chemistry, Manufacturing and Controls program summarized in the meeting package adequately supports filing and review of the NDA?

**RESPONSE:** The CMC program summary seems acceptable for filing and review. Please provide the following where applicable:

- Appropriate in-process controls during product manufacturing and (b) (4)
- In-use supporting data to demonstrate that drug substance particles are (b) (4) over the repeated gel-fluid-gel conversions during repeated drug product administration in the container configuration.
- Content uniformity for drug product specification at release and stability
- Justification for the 80.0-120.0% of label claim proposed for benzalkonium chloride assay
- Justification for the proposed acceptance criteria and test on particle size distribution in the drug product specification

- The acceptance criterion of NMT (b) (4) is recommended for any individual unspecified in the drug product specification.
- Leachable studies for (b) (4) container closure systems
- Stress studies for the drug product as per ICH guidance, e.g. degradation, photostability, etc.
- Temperature cycling studies for the drug product
- Reference ICH Q1A (R2) for selecting storage conditions for the stability protocol. (b) (4) RH is unacceptable as the alternate long-term or intermediate storage condition. The recommended alternate long-term storage condition is (b) (4) RH for (b) (4) containers.
- Use the worst scenario for the orientation (upright or horizontal) for future long-term stability.
- Please clarify if the manufacturing site for Phase 3 supplies will also be the commercial site. If it is not the same site, a bridging study may be necessary. SUPAC-SS contains examples, including in vitro release rate testing, for bridging different sites.

*Question #9* As indicated, the drug product met the definitions of a gel described in both USP and FDA Data manual. Does the Agency agree that the rationale and data provided in this meeting package is sufficient to grant this formulation a gel designation?

**RESPONSE:** The rationale and available data appear to support the gel designation. However, supporting data should be submitted to the NDA, and the appropriate dosage form descriptor will be evaluated during NDA review.

*Question #10* Does the Agency agree that the Administrative approach described above is adequate for a successful filing and review of the NDA?

**RESPONSE:** The proposed approach appears acceptable for filing the NDA. Final determination can only be made after the review of the NDA submission.

*Question #11* Does the Agency have any comments regarding the intended formats of

**RESPONSE:**

1. Provide all raw datasets, as well as analysis datasets (including all efficacy and safety variables) used to generate the results presented in your study report. In addition, provide a data definition file (in pdf format or xml format) that includes information on how efficacy variables are derived.
2. Include the programs used for creating main efficacy analysis datasets from submitted raw datasets and the programs used for the efficacy and main safety analyses. In addition, provide a document that explains what each program is used for.
3. You are encouraged to submit standardized datasets following the CDISC guidelines for SDTM and ADaM datasets. You are also encouraged to send a reviewer's guide explaining which variables in which datasets were used to generate the main efficacy and safety results..

4. You can check the FDA website to find the information about current document and guidance. Link to Study Data Specifications  
<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM199759.pdf>

**Discussion during the meeting:**

Bausch & Lomb asked whether the timeline of reviewing the Pediatric “Written Request” response was still 120 days. The Division responded that it was the goal.

**For question #5**

The Division is recommending stability testing to be performed at (b) (4) RH through expiry. Matrix design can be considered.

**For question #7**

The Division noted that it would be unlikely that a shelf life time would exceed more than one timepoint from the submitted real time stability data, even assuming the statistical evaluation and quality of the data are acceptable.

**For question #8, Bullet point 2:**

It was recommended that drug product attributes, e.g., drop weight, potency, particle size distribution, be evaluated. Such properties are expected to be retained though expiry. Results from multiple bottles and more than one batch are recommended.

**Bullet point 3:**

A similar approach for content uniformity to demonstrate the dose delivery throughout the bottle is consistent is recommended.

**Bullet point 6**

The acceptance criterion of NMT (b) (4) for any individual unspecified impurity is recommended. The Division suggested that the observed specified impurities can be listed by RRT and moved to a category of an individual specified impurity.

NDA expected arrival July 2011.

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/s/  
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WILEY A CHAMBERS  
04/29/2011

<b>For Internal Use Only</b>
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## Meeting Request Granted Form\*\*

(Use this form to document the meeting granted via telephone.)

Complete the information below and check form into DFS.

Application Type	P-IND	IND	NDA
Application Number	NDA 202872		
<b>DATE</b> Sponsor informed of meeting granted	March 1, 2011		
Sponsor was informed of: <ul style="list-style-type: none"> <li>• date/time &amp; meeting location</li> <li>• expected FDA attendees</li> <li>• meeting briefing package due date</li> <li>• number of copies</li> </ul>	<p>April 29, 2011 (9:00 – 10:00AM), BLDG #22, RM #1315</p> <p>Clinical, Chemistry, Pharmtox, &amp; Biopharm reviewers</p> <p>Yes (date: <u>March 25, 2011</u>)</p> <p>Requested 14 copies of the meeting pkg.</p> <p>Other: please indicate _____</p>		
Project Manager	Raphael Rodriguez		

\*\*Any follow-up letter must be checked into DFS as an advice letter, **NOT** as a meeting request granted letter.

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/s/  
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RAPHAEL R RODRIGUEZ  
03/25/2011

# ACTION PACKAGE CHECKLIST

## APPLICATION INFORMATION<sup>1</sup>

NDA # 202872 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: LOTEMAX Established/Proper Name: loteprednol etabonate ophthalmic gel Dosage Form: 0.5% gel		Applicant: Bausch and Lomb Agent for Applicant (if applicable):
RPM: June Germain		Division: Transplant and Ophthalmology Products
<p><b><u>NDA and NDA Efficacy Supplements:</u></b></p> <p>NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1)   <input type="checkbox"/> 505(b)(2)  Efficacy Supplement:   <input type="checkbox"/> 505(b)(1)   <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p><b><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></b></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> This application does not rely upon a listed drug.  <input type="checkbox"/> This application relies on literature.  <input type="checkbox"/> This application relies on a final OTC monograph.  <input type="checkbox"/> This application relies on (explain)</p> <p><b><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></b></p> <p><b><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></b></p> <p><input type="checkbox"/> No changes   <input type="checkbox"/> Updated   Date of check:</p> <p><b><u>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.</u></b></p>
❖ Actions		
<ul style="list-style-type: none"> <li>• Proposed action</li> <li>• User Fee Goal Date is <u>September 29, 2012</u></li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>• Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>		<input checked="" type="checkbox"/> None

<sup>1</sup> 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.

<sup>2</sup> For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a>). If not submitted, explain _____</p>	<input type="checkbox"/> Received
<p>❖ Application Characteristics<sup>3</sup></p>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only):</p> <p><input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch  <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch  <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510)  <input type="checkbox"/> Restricted distribution (21 CFR 314.520)          Subpart I <input type="checkbox"/> Approval based on animal studies</p> <p>BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41)  <input type="checkbox"/> Restricted distribution (21 CFR 601.42)          Subpart H <input type="checkbox"/> Approval based on animal studies</p> <p><input type="checkbox"/> Submitted in response to a PMR  <input type="checkbox"/> Submitted in response to a PMC  <input type="checkbox"/> Submitted in response to a Pediatric Written Request</p> <p>REMS: <input type="checkbox"/> MedGuide  <input type="checkbox"/> Communication Plan  <input type="checkbox"/> ETASU  <input type="checkbox"/> MedGuide w/o REMS  <input type="checkbox"/> REMS not required</p> <p>Comments:</p>	
<p>BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<input type="checkbox"/> Yes, dates
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> <li>Office of Executive Programs (OEP) liaison has been notified of action</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>Press Office notified of action (by OEP)</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>Indicate what types (if any) of information dissemination are anticipated</li> </ul>	<input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

<sup>3</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> <li>Is approval of this application blocked by any type of exclusivity?</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> <li>NDA 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.</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA/BLA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(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.)</li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(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.)</li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(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.)</li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>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.)</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> <li>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.</li> </ul>	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> <li>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.</li> </ul>	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> <li>[505(b)(2) applications] If the application includes a <b>paragraph III</b> 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).</li> </ul>	<input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> <li>[505(b)(2) applications] For <b>each paragraph IV</b> 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)).</li> </ul>	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

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

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

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

Yes  No

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

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

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

Yes  No

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

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

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

Yes  No

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

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

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

Yes  No

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

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

<p>(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?</p> <p>(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).</p> <p><i>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).</i></p> <p><i>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.</i></p>	<p><input type="checkbox"/> Yes    <input type="checkbox"/> No</p>
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**CONTENTS OF ACTION PACKAGE**

❖ Copy of this Action Package Checklist <sup>4</sup>	9-28-12
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
<b>Action Letters</b>	
❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	Action(s) and date(s) AP 9-28-12
<b>Labeling</b>	
❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
<ul style="list-style-type: none"> <li>• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	9-25-12
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	1-27-12
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	NDA 200738, NDA 20583

<sup>4</sup> Fill in blanks with dates of reviews, letters, etc.

Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling ( <i>write submission/communication date at upper right of first page of each piece</i> )	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> <li>Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	
<ul style="list-style-type: none"> <li>Example of class labeling, if applicable</li> </ul>	
❖ Labels ( <b>full color</b> carton and immediate-container labels) ( <i>write submission/communication date on upper right of first page of each submission</i> )	
<ul style="list-style-type: none"> <li>Most-recent draft labeling</li> </ul>	9-25-12, 4-13-12
❖ Proprietary Name <ul style="list-style-type: none"> <li>Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> <li>Review(s) (<i>indicate date(s)</i>)</li> <li>Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.</li> </ul>	acceptability 9-25-12, non-acceptability 1-31-12 Review 9-24-12,
❖ Labeling reviews ( <i>indicate dates of reviews and meetings</i> )	<input checked="" type="checkbox"/> RPM 2-17-12 <input checked="" type="checkbox"/> DMEPA 3-8-12 <input type="checkbox"/> DMPP/PLT (DRISK) <input checked="" type="checkbox"/> ODPD (DDMAC) 8-16-12 <input type="checkbox"/> SEALD <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
<b>Administrative / Regulatory Documents</b>	
❖ Administrative Reviews (e.g., RPM Filing Review <sup>5</sup> /Memo of Filing Meeting) ( <i>indicate date of each review</i> )	RPM filing review 2-17-12
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs (b)(2) Approvals Only: 505(b)(2) Assessment ( <i>indicate date</i> )	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary ( <i>signed by Division Director</i> )	<input type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	
<ul style="list-style-type: none"> <li>Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>This application is on the AIP <ul style="list-style-type: none"> <li>If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action
❖ Pediatrics ( <i>approvals only</i> ) <ul style="list-style-type: none"> <li>Date reviewed by PeRC <u>7-18-12</u> If PeRC review not necessary, explain: _____</li> <li>Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>)</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent ( <i>include certification</i> )	<input checked="" type="checkbox"/> Verified, statement is acceptable

<sup>5</sup> Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Outgoing communications ( <i>letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons</i> )	7-31-12, 5-17-12, 5-16-12, 2-7-12, 1-30-12, 1-6-11
❖ Internal memoranda, telecons, etc.	8-7-12, 8-1-12, 1-17-12
❖ Minutes of Meetings	
• Regulatory Briefing ( <i>indicate date of mtg</i> )	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting ( <i>indicate date of mtg</i> )	<input checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting ( <i>indicate date of mtg</i> )	<input type="checkbox"/> No mtg 4-29-11
• EOP2 meeting ( <i>indicate date of mtg</i> )	<input type="checkbox"/> No mtg 8-26-09
• Other milestone meetings (e.g., EOP2a, CMC pilots) ( <i>indicate dates of mtgs</i> )	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available ( <i>do not include transcript</i> )	
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Division Director Summary Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None Division Director summary 9-28-12, Deputy Director review 9-27-12
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 9-26-12
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input checked="" type="checkbox"/> None
<b>Clinical Information<sup>6</sup></b>	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) ( <i>indicate date for each review</i> )	
• Clinical review(s) ( <i>indicate date for each review</i> )	9-27-12, 2-28-12
• Social scientist review(s) (if OTC drug) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )	
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management	
• REMS Documents and Supporting Statement ( <i>indicate date(s) of submission(s)</i> )	
• REMS Memo(s) and letter(s) ( <i>indicate date(s)</i> )	
• Risk management review(s) and recommendations (including those by OSE and CSS) ( <i>indicate date of each review and indicate location/date if incorporated into another review</i> )	<input checked="" type="checkbox"/> None
❖ DSI Clinical Inspection Review Summary(ies) ( <i>include copies of DSI letters to investigators</i> )	<input type="checkbox"/> None requested 8-8-12, 8-3-12, 6-4-12

<sup>6</sup> Filing reviews should be filed with the discipline reviews.

<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
Clinical Microbiology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (indicate date for each review)	<input type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Statistical Review(s) (indicate date for each review)	<input type="checkbox"/> None 8-23-12, 1-25-12
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) (indicate date for each review)	<input type="checkbox"/> None 5-17-12
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters)	<input checked="" type="checkbox"/> None
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Supervisory Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	<input type="checkbox"/> None 8-24-12, 1-25-12
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (include copies of DSI letters)	<input checked="" type="checkbox"/> None requested
<b>Product Quality</b> <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Product quality review(s) including ONDQA biopharmaceutics reviews (indicate date for each review)	<input type="checkbox"/> None 8-17-12, 1-11-12
❖ Microbiology Reviews	<input type="checkbox"/> Not needed 8-9-12, 1-12-12
<input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (indicate date of each review)	
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) (indicate date of each review)	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review)	<input checked="" type="checkbox"/> None

❖ Environmental Assessment (check one) (original and supplemental applications)		
<input checked="" type="checkbox"/> Categorical Exclusion ( <i>indicate review date</i> )( <i>all original applications and all efficacy supplements that could increase the patient population</i> )		CMC 8-17- 12
<input type="checkbox"/> Review & FONSI ( <i>indicate date of review</i> )		
<input type="checkbox"/> Review & Environmental Impact Statement ( <i>indicate date of each review</i> )		
❖ Facilities Review/Inspection		
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout) ( <i>date completed must be within 2 years of action date</i> ) ( <i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>7</sup></i> )		Date completed: 3-20-12 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER ( <i>date of most recent TB-EER must be within 30 days of action date</i> ) ( <i>original and supplemental BLAs</i> )		Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation ( <i>check box only, do not include documents</i> )		<input checked="" type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

<sup>7</sup> I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

## Appendix to Action Package Checklist

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

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

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

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

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

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

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

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

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