

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-737**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

Bausch & Lomb, Inc.  
NDA 21-737  
Section 1.4: Patent Certification

Retisert™  
Fluocinolone Acetonide  
Intravitreal Implant, 0.59 mg

**PATENT OWNER STATEMENT**

Control Delivery Systems, Inc. acknowledges that it has a licensing agreement in effect with the applicant, Bausch & Lomb, for US Patent No.'s 6,375,972 and 6,217,895 and consents to an immediate effective date upon approval of this New Drug Application.

  
\_\_\_\_\_  
Paul Ashton, Ph.D.  
President  
Control Delivery Systems, Inc.

9/27/04  
Date

**PARAGRAPH IV PATENT CERTIFICATION**

Pursuant to 21 CFR 314.50(i)(3), Bausch & Lomb Incorporated is hereby submitting a Paragraph IV Patent Certification in accordance with 21 CFR 314.50(i)(1)(i)(A)(4).

The undersigned certifies that US Patent No.'s 6,548,078 and 6,217,895 will not be infringed by the manufacture, use, or sale of the drug, Retisert™, for which this application is submitted. Bausch & Lomb Incorporated has a licensing agreement with the patent owner, Dr. Paul Ashton of Control Delivery Systems, Inc.

In accordance with 21 CFR 314.52 (a), this notice will be sent by certified mail to Dr. Paul Ashton at Control Delivery Systems, Inc., the owner of the aforementioned patents. This notice will be sent by certified mail, return receipt requested, to Dr. Ashton.



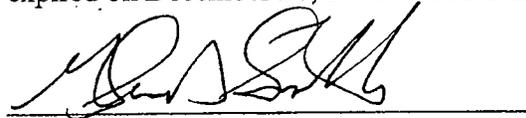
\_\_\_\_\_  
Glenn D. Smith  
Assistant Counsel  
Bausch & Lomb Incorporated

August 2, 2004  
Date

**PARAGRAPH II PATENT CERTIFICATION**

Pursuant to 21 CFR 314.50(i)(1)(i)(A)(2), Bausch & Lomb is hereby submitting a Paragraph II Patent Certification for our 505(b)2 application for the Retisert™ implant.

The undersigned certifies that, in its opinion and to the best of its knowledge, US Patent No.'s 3,014,938 and 3,126,375 covering the active ingredient, fluocinolone acetonide, expired on December 26, 1978 and March 24, 1981 respectively.



*Glenn D. Smith*  
*Assistant Counsel*  
*Bausch & Lomb Incorporated*

August 2, 2004  
*Date*

**PATENT INFORMATION**

Information is supplied for 2 patents as follows:

| Patent Number 6,548,078  |   |
|--------------------------|---|
| Date Patent will Expire: | March 22, 2019 subject to a terminal disclaimer   |
| Type of Patent:          | Method for treating and/or preventing retinal diseases with sustained release corticosteroids |
| Name of patent Owner:    | Control Delivery Systems, Inc.*   |

| Patent Number 6,217,895  |   |
|--------------------------|---|
| Date Patent will Expire: | March 22, 2019  |
| Type of Patent:          | Method for treating and/or preventing retinal diseases with sustained release corticosteroids |
| Name of patent Owner:    | Control Delivery Systems, Inc.*   |

*\*The assignee of the patents, Control Delivery Systems, Inc., has licensed the above referenced patents to Bausch & Lomb Incorporated.*

The undersigned declares that Patent No.'s 6,548,078 and 6,217,895 cover the formulation, composition, and method of use of the Fluocinolone Acetonide Intravitreal Implant. This product is currently the subject of this application for which approval is sought.



Glenn D. Smith  
Assistant Counsel  
Bausch & Lomb Incorporated

August 2, 2004

Date

**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

21-737

NAME OF APPLICANT / NDA HOLDER

Bausch & 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)

Retisert

ACTIVE INGREDIENT(S)

Fluocinolone Acetonide

STRENGTH(S)

0.59 mg

DOSAGE FORM

Intravitreal implant

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 file 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

6,217,895

b. Issue Date of Patent

4/17/2001

c. Expiration Date of Patent

3/22/2019

d. Name of Patent Owner

Control Delivery Systems, Inc.

Address (of Patent Owner)

400 Pleasant Street

City/State

Watertown, Massachusetts

ZIP Code

02472

FAX Number (if available)

(617) 926-5050

Telephone Number

(617) 926-5000

E-Mail Address (if available)

info@controldelivery.com

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

FAX Number (if available)

Telephone Number

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

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 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, 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 (as listed in the patent) 11 Does the patent claim 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 approved labeling.)  
The intended use is for treatment of non-infectious uveitis affecting the posterior segment of the eye.

**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



August 2, 2007

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

Glenn D. Smith

Address

Bausch & Lomb Incorporated  
One Bausch & Lomb Place

City/State

Rochester, New York

ZIP Code

14604-2701

Telephone Number

(585) 338-6142

FAX Number (if available)

(585) 338-8706

E-Mail Address (if available)

glenn.smith@bausch.com

The public reporting burden for this collection of information has been estimated to average 9 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:

Food and Drug Administration  
CDER (HFD-007)  
5600 Fishers Lane  
Rockville, MD 20857

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 supplemental 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. 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 July 2003) 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://forms.psc.gov/forms/fdahtm/fdahtm.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.

- 4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.

- 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

21-737

NAME OF APPLICANT / NDA HOLDER

Bausch & 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)

Retisert

ACTIVE INGREDIENT(S)  
Fluocinolone Acetonide

STRENGTH(S)  
0.59 mg

DOSAGE FORM

Intravitreal implant

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  
6,548,078

b. Issue Date of Patent  
4/15/2003

c. Expiration Date of Patent  
3/22/2019

d. Name of Patent Owner  
Control Delivery Systems, Inc.

Address (of Patent Owner)  
400 Pleasant Street

City/State  
Watertown, Massachusetts

ZIP Code  
02472

FAX Number (if available)  
(617) 926-5050

Telephone Number  
(617) 926-5000

E-Mail Address (if available)  
info@controldelivery.com

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

FAX Number (if available)

Telephone Number

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 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, 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 (as listed in the patent) 10, 30, 51 Does the patent claim 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 approved labeling.) The intended use is for treatment of non-infectious uveitis affecting the posterior segment of the eye.

**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.

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Date Signed



August 2, 2007

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  
Glenn D. Smith

Address  
Bausch & Lomb Incorporated  
One Bausch & Lomb Place

City/State  
Rochester, New York

ZIP Code  
14604-2701

Telephone Number  
(585) 338-6142

FAX Number (if available)  
(585) 338-8706

E-Mail Address (if available)  
glenn.smith@bausch.com

The public reporting burden for this collection of information has been estimated to average 9 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:

Food and Drug Administration  
CDER (HFD-007)  
5600 Fishers Lane  
Rockville, MD 20857

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

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- 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. 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 July 2003) 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://forms.psc.gov/forms/fdahm/fdahm.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.

- 4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.
- 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 FOR NDA # 21-737 SUPPL # \_\_\_\_\_

TradeName RETISERT

GenericName fluocinolone acetonide intravitreal implant 0.59mg

Applicant Name Bausch & Lomb HFD-550

Approval Date If Known April 8, 2005

**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 question about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?  
YES /XX/ 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 /XX / 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 / XX / NO /    /

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

**7 years - Designated Orphan drug Product**

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

YES /    / NO / XX /

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

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

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

YES /    / NO / XX /

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 / XX / NO / \_\_\_/

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

**NDA# 12-787** Synalar (fluocinolone acetonide) Cream, 0.025%, and Synemol (fluocinolone acetonide) Cream, 0.025%

**NDA# 13-960** Synalar (fluocinolone acetondie) Ointment, 0.025%

**NDA# 15-296** Synalar (fluocinolone acetonide) Topical Solution, 0.1%

**NDA# 19-452** Derma-Smooth/FS (fluocinolone acetonide) Topical Oil, 0.01%.

**NDA# 20-001** FS Shampoo, 0.01% (Fluocinolone acetonide) Topical 0.01%.

**NDA# 21-112** Trilumatm Cream (fluocinolone acetonide 0.01%, hydroquinone 4%, tretinoin 0.05%)

2. Combination product.

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

YES / \_\_\_ / NO / \_\_\_/

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

NDA#

NDA#

NDA#

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

**PART III THREE-YEAR EXCLUSIVITY FOR NDA'S 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 /\_XX\_/ 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 /\_XX\_/ 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 /XX/

(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 /XX/

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# BLP 415-001

---

Study# BLP 415-004

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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



Study# BLP 415-001

Study# BLP 415-004

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 !  
IND # 60,000 YES / XX / ! NO / \_\_\_ / Explain: \_\_\_\_\_  
!  
!  
Investigation #2 !  
IND # 60,000 YES / XX / ! 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 / \_\_\_ / Explain \_\_\_\_\_ ! NO / \_\_\_ / Explain \_\_\_\_\_  
!  
\_\_\_\_\_  
!  
\_\_\_\_\_  
!  
Investigation #2 !  
YES / \_\_\_ / Explain \_\_\_\_\_ ! NO / \_\_\_ / Explain \_\_\_\_\_  
!  
\_\_\_\_\_  
!  
\_\_\_\_\_

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

YES /\_\_\_/      NO /\_\_\_/

If yes, explain: \_\_\_\_\_  
\_\_\_\_\_

Signature \_\_\_\_\_ Date \_\_\_\_\_  
Raphael R. Rodriguez  
RPM

Signature \_\_\_\_\_ Date \_\_\_\_\_  
Lucious Lim, M.D.  
Clinical Reviewer

Signature \_\_\_\_\_ Date \_\_\_\_\_  
Wiley A. Chambers, M.D.  
Deputy Director

Form OGD-011347 Revised 05/10/2004

cc:  
Archival NDA 21-737  
HFD-550 /Division File  
HFD-550 /RPM / RodriguezR  
HFD-610/Mary Ann Holovac  
HFD-104/PEDS/T.Crescenzi

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

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Wiley Chambers  
4/8/05 05:49:13 PM

**PEDIATRIC PAGE**

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 21-737 Supplement Type (e.g. SE5): \_\_\_\_\_ Supplement Number: \_\_\_\_\_

Stamp Date: October 7, 2004 Action Date: April 8, 2005

HFD 550 Trade and generic names/dosage form: RETISERT (fluocinolone acetonide intravitreal implant) 0.59mg

Applicant: Bausch & Lomb, Inc. Therapeutic Class: 4041410 Corticosteroid

Indication(s) previously approved: None

Each approved indication must have pediatric studies: **Completed, Deferred, and/or Waived.**

Number of indications for this application(s): 1

Indication #1: *treatment of chronic non-infectious uveitis affecting the posterior segment of the eye.*

Is there a full waiver for this indication (check one)?

**XX Yes:** Please proceed to Section A.

**No:** Please check all that apply:  Partial Waiver  Deferred  Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

**Section A: Fully Waived Studies**

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns

**XX Other:** *Fluocinolone acetonide intravitreal implant for the posterior uveitis indication is exempted from the pediatric assessment requirement pursuant to 21 CFR §314.55(d) due to its orphan drug designation.*

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section B: Partially Waived Studies**

Age/weight range being partially waived:

|           |          |           |           |                    |
|-----------|----------|-----------|-----------|--------------------|
| Min _____ | kg _____ | mo. _____ | yr. _____ | Tanner Stage _____ |
| Max _____ | kg _____ | mo. _____ | yr. _____ | Tanner Stage _____ |

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: \_\_\_\_\_

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

**Section C: Deferred Studies**

Age/weight range being deferred:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: \_\_\_\_\_

Date studies are due (mm/dd/yy): \_\_\_\_\_

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

**Section D: Completed Studies**

Age/weight range of completed studies:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Raphael R. Rodriguez \_\_\_\_\_  
Regulatory Project Manager

Lucious Lim, M.D. \_\_\_\_\_  
Clinical Reviewer

Wiley A. Chambers, M.D. \_\_\_\_\_  
Deputy Director, HFD-550

cc: NDA 21-737  
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

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

-----  
Wiley Chambers  
4/8/05 05:48:09 PM

**BAUSCH  
& LOMB**

**DEBARMENT CERTIFICATION**

Pursuant to Section 306(k)(1) of the Federal Food, Drug and Cosmetic Act, Bausch & Lomb certifies that it did not and will not use in any capacity in connection with this application the services of persons listed pursuant to Section 306(e) as debarred under subsections 306(a) or (b) of the Act.

*Sally J. Millick*

\_\_\_\_\_  
Sally J. Millick  
Manager, Strategic Staffing  
Corporate Human Resources  
Bausch & Lomb

*4/29/04*

\_\_\_\_\_  
Date

### 1.9 FINANCIAL DISCLOSURE

Forms FDA 3454 are provided for the following clinical studies:

BLP 415-001

BLP 415-004

Forms FDA 3455 are provided for the following principal investigators:

BLP 415-001: Jaffe, Glenn; Kuppermann, Baruch; Martin, Daniel

BLP 415-004: Devenyi, Robert

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Food and Drug Administration  
**CERTIFICATION: FINANCIAL INTERESTS AND  
ARRANGEMENTS OF CLINICAL INVESTIGATORS**

Form Approved: OMB No. 0910-0396  
Expiration Date: February 28, 2006.

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

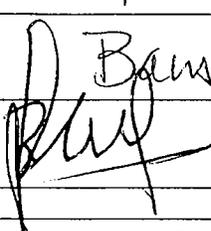
Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

|                        |           |  |
|------------------------|-----------|--|
| Clinical Investigators | Attached. |  |
|                        |           |  |
|                        |           |  |

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

|  |  |
|--|--|
| NAME<br>Brian Levy   | TITLE<br>Corporate VP<br>& Chief Medical Officer |
| FIRM / ORGANIZATION<br>Bausch + Lomb, Inc.   |  |
| SIGNATURE<br> | DATE<br>5/20/2004                                |

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Department of Health and Human Services  
Food and Drug Administration  
5600 Fishers Lane, Room 14C-03  
Rockville, MD 20857

**Clinical Study BLP 415-001**  
**Investigators and Subinvestigators with no Financial Interest**

---

- Investigator/Subinvestigators
- 1 Anand, Rajiv
- 
- 2 Berger, Brian B.
- 
- 3 Callanan, David
- 
- 4 Chalam, Kakarla V.
- 
- 5 Chee, Soon Phaik
- 
- 6 Davis, Janet
- 

- Investigator/Subinvestigators
- 7 Dugel, Pravin
- 
- 8 Dunn, James P.
- 
- 9 Foster, C. Stephen
- 
- 10 Freeman, Bill
- 
- 11 Goldstein, Debra A.
-

**Clinical Study BLP 415-001**  
**Investigators and Subinvestigators with no Financial Interest**

---

Investigator/Subinvestigators  
12 Ho, Allen C.

*[Handwritten scribble]*

13 Site #122

*[Handwritten scribble]*

Investigator/Subinvestigators

*[Handwritten scribble]*

14 Site #123

*[Handwritten scribble]*

15 Latkany, Paul

nica

16 Lowder, Careen Y.

*[Handwritten scribble]*

17 Site #125

*[Handwritten scribble]*

*[Handwritten scribble]*

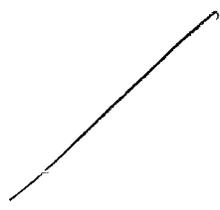
**Clinical Study BLP 415-001**  
**Investigators and Subinvestigators with no Financial Interest**

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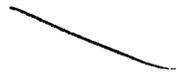
Investigator/Subinvestigators

  
18 Merrill, Pauline

  
19 Moorthy, Ramana S.

  
20 Morse, Lawrence S.

  
21 Noorily, Stuart W.

  
22 Pavan, Peter

Investigator/Subinvestigators

  
23 Raizman, Michael B.

  
24 Rosenbaum, James T.

  
25 Sheppard, John D.

  
26 VanGelder, Russell N.

  
27 Kang / Vitale, Albert

1   Page(s) Withheld

  8   § 552(b)(4) Trade Secret / Confidential

       § 552(b)(4) Draft Labeling

       § 552(b)(5) Deliberative Process

*Withheld Track Number: Administrative-\_\_\_\_\_*

# CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

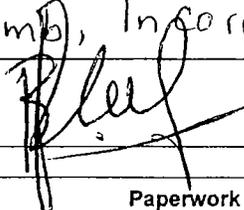
With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

|                        |           |  |
|------------------------|-----------|--|
| Clinical Investigators | Attached. |  |
|                        |           |  |
|                        |           |  |

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

|  |  |
|--|--|
| NAME<br>Brian Ley  | TITLE<br>Corporate VP<br>& Chief Medical Officer |
| FIRM / ORGANIZATION<br>Bausch + Lomb, Incorporated   |  |
| SIGNATURE<br> | DATE<br>5/20/2004                                |

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Department of Health and Human Services  
Food and Drug Administration  
5600 Fishers Lane, Room 14C-03  
Rockville, MD 20857

**Clinical Study BLP 415-004**  
**Investigators and Subinvestigators with no Financial Interest**

**Investigator/Subinvestigators**

1 Aaberg, Thomas Jr.

2 Biswas, J.

3 Conrad, Diane

4 Deschenes, Jean

5 Site #146952

6 Garg, S.P.

7 Hodge, William

8 Hooper, Phil

9 Lam, Dennis

**Investigator/Subinvestigators**

10 Lopez, Juan

11 Maturi, Raj K.

12 McCluskey, Peter

14 Perez-Ortiz, Don J.

15 Rabinovitch, Theodore

16 Rodden, William S.

18 Sangwan, Virendra S.

19 Stawell, Richard

20 Tay-Kearney, Mei-Ling

21 Uy, Harvey S.

### DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

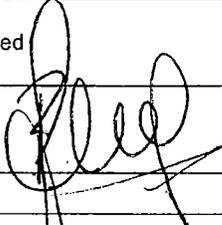
TO BE COMPLETED BY APPLICANT

The following information concerning \_\_\_\_\_, who participated as a clinical investigator in the submitted study \_\_\_\_\_, is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkboxes.

- any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;
- any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;
- any proprietary interest in the product tested in the covered study held by the clinical investigator;
- any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

|  |   |
|--|---|
| NAME<br>Brian Levy O.D.  | TITLE<br>Corporate Vice President and Chief Medical Officer |
| FIRM/ORGANIZATION<br>Bausch & Lomb, Incorporated   |   |
| SIGNATURE<br> | DATE<br>6/1/2004  |

#### Paperwork Reduction Act Statement

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. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to:

Department of Health and Human Services  
Food and Drug Administration  
5600 Fishers Lane, Room 14-72  
Rockville, MD 20857

**BAUSCH  
& LOMB**

# Memo

To: FDA  
From: Dan Donatello  
CC: Central File  
Date: 5/26/2004  
Re: Disclosure of Financial Interest and Arrangement for

M.D. is currently a \_\_\_\_\_ study, in which he enrolled \_\_\_\_\_ were enrolled, in total, in this study.

At the time of \_\_\_\_\_ initial involvement with \_\_\_\_\_, he disclosed to B&L a financial relationship with \_\_\_\_\_, the manufacturer of the FA implant used in the \_\_\_\_\_ study. Per Dr. \_\_\_\_\_ he has received a gift from \_\_\_\_\_ in an amount greater than \$25,000 to fund ongoing research and; also received a stock grant from \_\_\_\_\_ in an amount greater than \$50,000, both within one year of his participation in the \_\_\_\_\_ study. Dr. \_\_\_\_\_ informed the Duke Conflict of Interest Committee of this financial interest. To minimize any real or perceived bias, the Conflict of Interest committee has allowed Dr. \_\_\_\_\_ to continue as \_\_\_\_\_ study, provided that an independent grader records the measurement of anterior chamber cells and vitreous opacity (subjective measurements).

In the beginning of 2004, Dr. \_\_\_\_\_ received an unrestricted gift from B&L in the amount of \$62,000. Up to this point, Dr. \_\_\_\_\_ did not have any direct financial relationship with Bausch and Lomb. However, as described above, measures to minimize study bias were already in place at the time the gift was received.

### DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

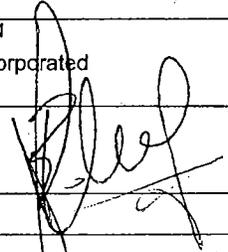
TO BE COMPLETED BY APPLICANT

The following information concerning \_\_\_\_\_, who participated as a clinical investigator in the submitted study \_\_\_\_\_, is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkboxes.

- any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;
- any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;
- any proprietary interest in the product tested in the covered study held by the clinical investigator;
- any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

|  |   |
|--|---|
| NAME<br>Brian Levy O.D.  | TITLE<br>Corporate Vice President and Chief Medical Officer |
| FIRM/ORGANIZATION<br>Bausch & Lomb, Incorporated   |   |
| SIGNATURE<br> | DATE<br>6/1/2004  |

#### Paperwork Reduction Act Statement

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. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to:

Department of Health and Human Services  
Food and Drug Administration  
5600 Fishers Lane, Room 14-72  
Rockville, MD 20857

**BAUSCH  
& LOMB**

# Memo

To: FDA  
From: Daniel Donatello  
CC: \_\_\_\_\_ 1 Central File  
Date: 5/27/2004  
Re: Disclosure of Financial Interest and Arrangement for \_\_\_\_\_

\_\_\_\_\_ M.D. is currently a \_\_\_\_\_ in  
which he enrolled \_\_\_\_\_ patients were enrolled in total  
in this study.

Dr. \_\_\_\_\_ is concurrently serving \_\_\_\_\_ Incorporated.  
For his ongoing consulting services for B&L, Dr. \_\_\_\_\_ is receiving an honorarium of  
US \$30,000/year.

Due to the fact that Dr. \_\_\_\_\_ enrolled only \_\_\_\_\_ into this study, it is unlikely that  
his clinical study results can bias the study outcome.

## DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

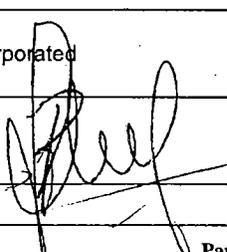
TO BE COMPLETED BY APPLICANT

The following information concerning \_\_\_\_\_, who participated as a clinical investigator in the submitted study \_\_\_\_\_, is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkboxes.

- any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;
- any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;
- any proprietary interest in the product tested in the covered study held by the clinical investigator;
- any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

|  |   |
|--|---|
| NAME<br>Brian Levy O.D.  | TITLE<br>Corporate Vice President and Chief Medical Officer |
| FIRM/ORGANIZATION<br>Bausch & Lomb, Incorporated   |   |
| SIGNATURE<br> | DATE<br>6/1/2004  |

### Paperwork Reduction Act Statement

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. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to:

Department of Health and Human Services  
Food and Drug Administration  
5600 Fishers Lane, Room 14-72  
Rockville, MD 20857

**BAUSCH  
& LOMB**

# Memo

To: FDA  
From: Daniel Donatello  
CC: \_\_\_\_\_ Central File  
Date: 5/27/2004  
Re: Disclosure of Financial Interest and Arrangement for \_\_\_\_\_

\_\_\_\_\_ M.D. is currently a \_\_\_\_\_ study, in which he enrolled \_\_\_\_\_ were enrolled in total in this study.

\_\_\_\_\_ For his ongoing consulting services for B&L, Dr. \_\_\_\_\_ is receiving an honorarium of US \$30,000/year.

Per \_\_\_\_\_, he has notified the \_\_\_\_\_ of his consulting contract with B&L. \_\_\_\_\_ has not found it necessary to institute any measures to minimize potential bias due to the relatively small number of patients enrolled by Dr. \_\_\_\_\_

# DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concerning \_\_\_\_\_, who participated as a clinical investigator in the submitted study \_\_\_\_\_, is submitted in accordance with 21 CFR part \_\_\_\_\_.

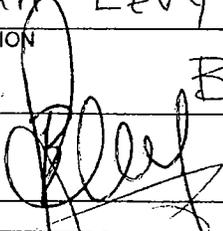
Name of clinical investigator  
Name of clinical study

54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkboxes.

- any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;
- any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;
- any proprietary interest in the product tested in the covered study held by the clinical investigator;
- any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

|                     |   |       |   |
|---------------------|---|-------|---|
| NAME                | Brian Levy  | TITLE | Corporate VP<br>and Chief Medical Officer |
| FIRM / ORGANIZATION | Bausch + Lomb, Inc  |       |   |
| SIGNATURE           |  | DATE  | 5/20/2004                                 |

### Paperwork Reduction Act Statement

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. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to:

Department of Health and Human Services  
Food and Drug Administration  
5600 Fishers Lane, Room 14-72  
Rockville, MD 20857





**Bausch & Lomb™**

8500 Hidden River Parkway  
Tampa, FL 33637  
813.975.7700  
www.bausch.com

April 07, 2005

Wiley Chambers, M.D., Deputy Director  
Division of Anti-Inflammatory, Analgesic, and  
Ophthalmologic Drug Products (HFD-550)  
Center for Drug Evaluation and Research  
FOOD AND DRUG ADMINISTRATION  
Attention: Central Document Room  
9201 Corporate Blvd  
Rockville, MD 20850

**RE: NDA 21-737**  
**Fluocinolone Acetonide Intravitreal Implant (Retisert™)**  
**Revisions to Package Insert Submitted on 03/31/05**

Dear Dr. Chambers:

Reference is made to our pending Fast Track NDA 21-737 for the above referenced drug product for the treatment of noninfectious uveitis affecting the posterior segment of the eye. The complete NDA was filed on 10/07/05.

We have noted two errors in the package insert submitted to FDA on 03/31/05 subsequent to our labeling discussion with FDA on the same day. The errors have been corrected in the attached revised version of the package insert. The following necessary changes are proposed:

- 

- 

Attached please find the corrected package insert text. The proposed changes are highlighted for ease of review.

The required archival and review copies of this submission are being sent to the Central Document Room. An electronic desk copy of this submission is being sent to the attention of Project Manager Raphael Rodriguez for distribution.

The information in this submission is confidential and as such should be handled in accordance with the provisions established under 21 CFR 314.430.

If you have any questions regarding this correspondence, please contact me at (813) 866-2568 or by facsimile at (813) 975-7757 or by e-mail at [yelen\\_concepcion@bausch.com](mailto:yelen_concepcion@bausch.com).

Sincerely,

*Yelen Concepcion*

Yelen Concepcion

Manager, Regulatory Affairs – Pharmaceuticals

**Bausch & Lomb™**

8500 Hidden River Parkway  
Tampa, FL 33637  
813.975.7700  
www.bausch.com

April 5, 2005

Wiley Chambers, M.D., Deputy Director  
Division of Anti-Inflammatory, Analgesic, and  
Ophthalmologic Drug Products (HFD-550)  
Center for Drug Evaluation and Research  
FOOD AND DRUG ADMINISTRATION  
Attention: Central Document Room  
9201 Corporate Blvd  
Rockville, MD 20850

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N-000(4S)

**RE: NDA 21-737**  
**Fluocinolone Acetonide Intravitreal Implant (Retisert™)**  
**Phase 4 Commitments Proposal**

ORIG AMENDMENT

Dear Dr. Chambers:

Reference is made to our pending Fast Track NDA 21-737 for the above referenced drug product for the treatment of noninfectious uveitis affecting the posterior segment of the eye. The complete NDA was filed on 10/07/04.

Please find attached our proposals for the required Phase 4 Commitments received from FDA via e-mail on 3/31/04 and that were also discussed with FDA during the labeling teleconference that took place on the same day. Note that FDA comments are in bold and italics followed by our comments (unbolded).

The required archival and review copies of this submission are being sent to the Central Document Room. In addition, an electronic copy is being sent to the attention of Project Manager Raphael Rodriguez for distribution.

The information in this submission is confidential and as such should be handled in accordance with the provisions established under 21 CFR 314.430.

If you have any questions regarding this correspondence, please contact me at (813) 866-2568 or by facsimile at (813) 975-7757 or by e-mail at yelen\_concepcion@bausch.com.

Sincerely,

*Yelen Concepcion*

Yelen Concepcion  
Manager, Regulatory Affairs – Pharmaceuticals

ORIGINAL

DUPLICATE

**Bausch & Lomb™**

8500 Hidden River Parkway  
Tampa, FL 33637  
813.975.7700  
www.bausch.com

March 31, 2005

Wiley Chambers, M.D., Deputy Director  
Division of Anti-Inflammatory, Analgesic, and  
Ophthalmologic Drug Products (HFD-550)  
Center for Drug Evaluation and Research  
FOOD AND DRUG ADMINISTRATION  
Attention: Central Document Room  
9201 Corporate Blvd  
Rockville, MD 20850

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APR 04 2005

MEGA / CDER

ORIG AMENDMENT  
N-000(BL)

**RE: NDA 21-737**  
**Fluocinolone Acetonide Intravitreal Implant (Retisert™)**  
**Package Insert Text per 03/31/05 Labeling Teleconference with FDA**  
**Proposed Pouch and Carton Labeling**

Dear Dr. Chambers:

Reference is made to our pending Fast Track NDA 21-737 for the above referenced drug product for the treatment of noninfectious uveitis affecting the posterior segment of the eye. The complete NDA was filed on 10/07/05.

Further to today's teleconference with FDA to finalize the package insert (PI), we are providing a copy of the PI text as agreed upon during the meeting (see Attachment I). As discussed during our teleconference, we are also providing proposed labeling for the pouch and carton. The changes being proposed for the pouch and carton labeling are consistent with FDA recommendations for the "Description" section of the PI. In addition, we have added the patent numbers reflected on the PI to the pouch label (see Attachment II).

The required archival and review copies of this submission are being sent to the Central Document Room. An electronic desk copy of this submission is being to the attention of Project Manager Raphael Rodriguez for distribution.

The information in this submission is confidential and as such should be handled in accordance with the provisions established under 21 CFR 314.430.

If you have any questions regarding this correspondence, please contact me at (813) 866-2568 or by facsimile at (813) 975-7757 or by e-mail at yelen\_concepcion@bausch.com.

Sincerely,

*Yelen Concepcion*

Yelen Concepcion  
Manager, Regulatory Affairs - Pharmaceuticals

**Bausch & Lomb™**

8500 Hidden River Parkway  
Tampa, FL 33637  
813.975.7700  
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March 28, 2005

Wiley Chambers, M.D., Deputy Director  
Division of Anti-Inflammatory, Analgesic, and  
Ophthalmologic Drug Products (HFD-550)  
Center for Drug Evaluation and Research  
FOOD AND DRUG ADMINISTRATION  
Attention: Central Document Room  
9201 Corporate Blvd  
Rockville, MD 20850

**RE: NDA 21-737  
Fluocinolone Acetonide Intravitreal Implant (Retisert™)  
Proposed Package Insert Text**

Dear Dr. Chambers:

Reference is made to our pending Fast Track NDA 21-737 for the above referenced drug product for the treatment of noninfectious uveitis affecting the posterior segment of the eye. The complete NDA was filed on 10/07/05.

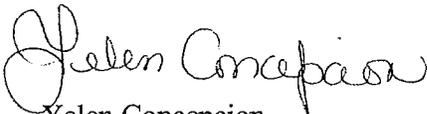
Bausch & Lomb has reviewed the package insert text received via e-mail from FDA on 03/18/05. Attached, please find our comments/proposals for the package insert based on the text received from FDA. As noted in Attachment I to this correspondence, there are some issues that Bausch & Lomb would like to clarify and/or further discuss in more detail with the FDA. Consequently, we request an official teleconference with the Division to come to a mutual understanding and promptly finalize the package insert.

The required archival and review copies of this submission are being sent to the Central Document Room. An electronic desk copy of this submission is being sent to the attention of Project Manager Raphael Rodriguez for distribution.

The information in this submission is confidential and as such should be handled in accordance with the provisions established under 21 CFR 314.430.

If you have any questions regarding this correspondence, please contact me at (813) 866-2568 or by facsimile at (813) 975-7757 or by e-mail at yelen\_concepcion@bausch.com.

Sincerely,



Yelen Concepcion  
Manager, Regulatory Affairs – Pharmaceuticals



**Bausch & Lomb™**

8500 Hidden River Parkway  
Tampa, FL 33637  
813.975.7700  
www.bausch.com

March 17, 2005

Wiley Chambers, M.D., Deputy Director  
Division of Anti-Inflammatory, Analgesic, and  
Ophthalmologic Drug Products (HFD-550)  
Center for Drug Evaluation and Research  
FOOD AND DRUG ADMINISTRATION  
Attention: Central Document Room  
9201 Corporate Blvd  
Rockville, MD 20850

**RE: NDA 21-737**  
**Fluocinolone Acetonide Intravitreal Implant (Retisert™)**  
**Response to 03/15/05 FDA Request for Information**

Dear Dr. Chambers:

Reference is made to our pending Fast Track NDA 21-737 for the above referenced drug product for the treatment of noninfectious uveitis affecting the posterior segment of the eye. The complete NDA was filed on 10/07/04.

In response to a request for information received via e-mail from the Medical Officer on 03/15/05, we are providing a table that summarizes the clinical studies in which the following 0.59 mg lots were used:

- Lot 00040
- Lot 00051A and 00051B
- Lot 02-0065

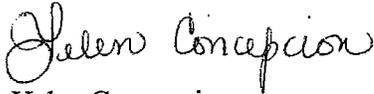
Refer to the attached for a complete response. For ease of review, the FDA question is provided in bold and italics, followed by our response (unbolded).

The required archival and review copies of this submission are being sent to the Central Document Room. In addition, an electronic copy is being sent to Project Manager Raphael Rodriguez for distribution to the Medical Officer.

The information in this submission is confidential and as such should be handled in accordance with the provisions established under 21 CFR 314.430.

If you have any questions regarding this correspondence, please contact me at (813) 866-2568 or by facsimile at (813) 975-7757 or by e-mail at [yelen\\_concepcion@bausch.com](mailto:yelen_concepcion@bausch.com).

Sincerely,



Yelen Concepcion  
Manager, Regulatory Affairs – Pharmaceuticals

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March 14, 2005

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Mr. Russ Livermore  
Electronic Document Room  
Center for Drug Evaluation and Research  
FOOD AND DRUG ADMINISTRATION  
Attention: Central Document Room  
5901-B Ammendale Road  
Beltsville, MD 20705

ORIG AMENDMENT

N-000-BS

**RE: NDA 21-737  
Fluocinolone Acetonide Intravitreal Implant (Retisert™)  
Resubmission of Additional CRF's submitted February 23, 2005: BLP 415-001 and BLP 415-004**

Dear Mr. Livermore:

Reference is made to a facsimile that Bausch & Lomb received from the CDER Electronic Document Room staff dated March 3, 2005, requesting the resubmission of the electronic CRF files, which Bausch & Lomb originally submitted to the FDA on February 23, 2005, due to corruption of the files on the CD.

Per our telephone conversation of March 11, 2005, enclosed please find our resubmission of a CD with the above-referenced CRF's. This CD was made this morning and every file was opened and viewed on a different computer. Included on this CD is a table of contents (refer to the "20050223 additional random CRFs" file). This table of contents was submitted as hard copy with the original CD on February 23<sup>rd</sup>.

The information in this submission is confidential and as such should be handled in accordance with the provisions established under 21 CFR 314.430.

If you have any problems with this CD, please don't hesitate to contact me at (813) 866-2568, by facsimile at (813) 975-7757, or by e-mail at yelen\_concepcion@bausch.com.

Sincerely,



Yelen Concepcion  
Manager, Regulatory Affairs – Pharmaceuticals

Enclosure: CD with CRF's for BLP 415-001 and BLP 415-004 (archival copy only)



**Bausch & Lomb™**

8500 Hidden River Parkway  
Tampa, FL 33637  
813.975.7700  
www.bausch.com

March 8, 2005

Wiley Chambers, M.D., Deputy Director  
Division of Anti-Inflammatory, Analgesic, and  
Ophthalmologic Drug Products (HFD-550)  
Center for Drug Evaluation and Research  
FOOD AND DRUG ADMINISTRATION  
Attention: Central Document Room  
9201 Corporate Blvd  
Rockville, MD 20850

**RE: NDA 21-737**  
**Fluocinolone Acetonide Intravitreal Implant (Retisert™)**  
**Microbiology Amendment: Addendum to Report RET-M-095**

Dear Dr. Chambers:

Reference is made to our pending Fast Track NDA 21-737 for the above referenced drug product for the treatment of noninfectious uveitis affecting the posterior segment of the eye. The complete NDA was filed on October 7, 2004.

In response to a request received on 03/04/05 from Dr. Pawar, microbiology reviewer, we are amending the above referenced NDA to provide additional data generated in support of a minimum sterilization dose of 25 kGy. The attached addendum to Report RET-M-095

\_\_\_\_\_") summarizes results of additional testing conducted by B&L providing further documentation of the log linear inactivation of Retisert implants inoculated with a high number of \_\_\_\_\_ resistant to \_\_\_\_\_

The required archival and review copy of this submission are being sent to the Central Document Room. In addition, an electronic copy of this submission is being sent to Dr. Pawar.

In accordance with 21 CFR 314.60(c), we certify that a true copy of the information contained in this amendment has been forwarded to FDA's Orlando District Office.

The information in this submission is confidential and as such should be handled in accordance with the provisions established under 21 CFR 314.430.

Please contact the undersigned should you have any questions and or comments regarding this correspondence.

Sincerely,

*Alicia Jones for Yelen Concepcion*

Yelen Concepcion

Manager, Regulatory Affairs – Pharmaceuticals

Telephone: (813) 866-2568

Facsimile: (813) 975-7757

e-mail: yelen\_concepcion@bausch.com

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ORIG AMENDMENT

N-000-(Be)

March 7, 2005

Wiley Chambers, M.D., Deputy Director  
Division of Anti-Inflammatory, Analgesic, and  
Ophthalmologic Drug Products (HFD-550)  
Center for Drug Evaluation and Research  
FOOD AND DRUG ADMINISTRATION  
Attention: Central Document Room  
9201 Corporate Blvd  
Rockville, MD 20850

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MAR 08 2005

MEGA / CDER

**RE: NDA 21-737**  
**Fluocinolone Acetonide Intravitreal Implant (Retisert™)**  
**CMC Amendment per 02/23/05 Teleconference with FDA - Part II**

Dear Dr. Chambers:

Reference is made to our pending Fast Track NDA 21-737 for the above referenced drug product for the treatment of noninfectious uveitis affecting the posterior segment of the eye. The complete NDA was filed on 10/07/04.

As a follow up to our submission of 02/28/05 and further to a teleconference with Chemistry Reviewer Dr. Su Tso on 02/23/05, we are amending the CMC section of our application to provide updated control documents as follows:

- Updated drug product release specifications and test methods
- Updated stability protocols
- Updated drug substance assay validation and test methods

Additionally, we are providing updated specifications for the ID test of silicone elastomer arrays (see Attachment 6), and raw material specifications for the unprinted foil pouches and adhesive label (see Attachment 7 for more details).

The required archival and review copies of this submission are being sent to the Central Document Room. In addition, an electronic copy of this submission is being sent to Dr. Tso.

In accordance with 21 CFR 314.60(c), we certify that a true copy of the information contained in this amendment has been forwarded to FDA's Orlando District Office.

The information in this submission is confidential and as such should be handled in accordance with the provisions established under 21 CFR 314.430.

Please contact the undersigned should you have any questions and or comments regarding this correspondence.

Sincerely,

*Yelen Concepcion*

Yelen Concepcion  
Manager, Regulatory Affairs – Pharmaceuticals  
Telephone: (813) 866-2568  
Facsimile: (813) 975-7757  
e-mail: yelen\_concepcion@bausch.com

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March 03, 2005

Wiley Chambers, M.D., Deputy Director  
Division of Anti-Inflammatory, Analgesic, and  
Ophthalmologic Drug Products (HFD-550)  
Center for Drug Evaluation and Research  
FOOD AND DRUG ADMINISTRATION  
Attention: Central Document Room  
9201 Corporate Blvd  
Rockville, MD 20850

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MAR 04 2005

MEGA / CDER

**RE: NDA 21-737**  
**Fluocinolone Acetonide Intravitreal Implant (Retisert™)**  
**Response to Clinical Reviewer's Request of 02/28/05**

ORIG AMENDMENT  
N-000-(BM)

Dear Dr. Chambers:

Reference is made to our pending Fast Track NDA 21-737 for the above referenced drug product for the treatment of noninfectious uveitis affecting the posterior segment of the eye. The complete NDA was filed on 10/07/05.

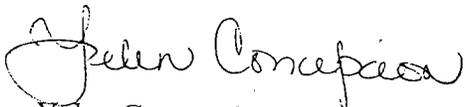
Provided in this submission are tables that summarize information requested via e-mail by Clinical Reviewer Dr. Lim on 02/28/05. To facilitate review, FDA questions are reproduced in bold and italics, followed by our responses (unbolded).

The required archival and review copies of this submission are being sent to the Central Document Room. In addition, an electronic copy is being sent to Dr. Lim.

The information in this submission is confidential and as such should be handled in accordance with the provisions established under 21 CFR 314.430.

If you have any questions regarding this correspondence, please contact me at (813) 866-2568 or by facsimile at (813) 975-7757 or by e-mail at [yelen\\_concepcion@bausch.com](mailto:yelen_concepcion@bausch.com).

Sincerely,



Yelen Concepcion  
Manager, Regulatory Affairs – Pharmaceuticals



**Bausch & Lomb™**

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8500 Hidden River Parkway  
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February 28, 2005

Wiley Chambers, M.D., Deputy Director  
Division of Anti-Inflammatory, Analgesic, and  
Ophthalmologic Drug Products (HFD-550)  
Center for Drug Evaluation and Research  
FOOD AND DRUG ADMINISTRATION  
Attention: Central Document Room  
9201 Corporate Blvd  
Rockville, MD 20850

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MAR 02 2005

MEGA / CDER

**RE: NDA 21-737**  
**Fluocinolone Acetonide Intravitreal Implant (Retisert™)**  
**CMC Amendment per 02/23/05 Teleconference with FDA**

Dear Dr. Chambers:

Reference is made to our pending Fast Track NDA 21-737 for the above referenced drug product for the treatment of noninfectious uveitis affecting the posterior segment of the eye. The complete NDA was filed on 10/07/04.

Further to a teleconference with Chemistry Reviewer Dr. Su Tso held on 02/23/05, we are updating the CMC section of our application to provide the following:

- Updated drug product release and stability specifications per FDA's recommendations
- Clearer chromatograms for drug substance assay, drug product assay, and release rate test methods
- Limit of Quantitation (LOQ) evaluation and associated chromatograms for drug substance assay method

The updated documentation referenced above is included in Appendices 1-3 of this submission. As agreed upon with Dr. Tso, pertinent control documents will be updated to include this new information and will be submitted to FDA as soon as they are available.

Additionally, we have become aware of an inadvertent error in the updated overall process flow chart submitted to FDA on 01/31/05. Refer to Appendix 4 of this submission for a corrected flow chart.

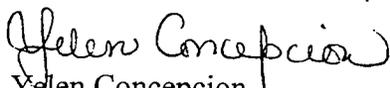
The required archival and review copies of this submission are being sent to the Central Document Room. In addition, an electronic copy of this submission is being sent to Dr. Tso.

In accordance with 21 CFR 314.60(c), we certify that a true copy of the information contained in this amendment has been forwarded to FDA's Orlando District Office.

The information in this submission is confidential and as such should be handled in accordance with the provisions established under 21 CFR 314.430.

Please contact the undersigned should you have any questions and or comments regarding this correspondence.

Sincerely,



Yelen Concepcion

Manager, Regulatory Affairs – Pharmaceuticals

Telephone: (813) 866-2568

Facsimile: (813) 975-7757

e-mail: yelen\_concepcion@bausch.com

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February 24, 2005

Wiley Chambers, M.D., Deputy Director  
Division of Anti-Inflammatory, Analgesic, and  
Ophthalmologic Drug Products (HFD-550)  
Center for Drug Evaluation and Research  
FOOD AND DRUG ADMINISTRATION  
Attention: Central Document Room  
9201 Corporate Blvd  
Rockville, MD 20850

**RECEIVED**

**FEB 25 2005**

**MEGA / CDER**

**ORIG AMENDMENT**

**N-000(SU)**

**RE: NDA 21-737**

**Fluocinolone Acetonide Intravitreal Implant (Retisert™)**

**4-Month Safety Update: Updated AE Incidence Tables per FDA Request**

Dear Dr. Chambers:

Reference is made to our pending Fast Track NDA 21-737 for the above referenced drug product for the treatment of noninfectious uveitis affecting the posterior segment of the eye. The complete NDA was filed on October 7, 2004.

In response to a request from Clinical Reviewer Dr. Lim, we are amending the above referenced NDA to provide updated AE incidence summary tables for the 4-Month Safety Update submitted to FDA on February 07, 2005. AE incidence tables provided in the update combined the serious and non-serious adverse events. Clinical Reviewer Dr. Lim asked on February 03, 2005, that AE incidence summary tables for our two pivotal studies, BLP 415-001 and BLP 415-004, to be included in the update, should be separated into serious and non-serious adverse events.

This submission provides, for each of the pivotal studies, the non-serious AE's through June 30, 2004, as separate tables which include ocular non-serious AE's (study eye and fellow eye) and non-ocular non-serious AE's. Additionally, incidence summary tables of ocular (study eye and fellow eye) and non-ocular non-serious AE's through June 30, 2004 are provided for both studies combined. Separate incidence summary tables for serious adverse events (SAE's) through June 30, 2004, were provided in the original 4-Month Safety Update submission on February 07, 2005, and are not reproduced in this submission. Also included are separate incidence summary tables of serious and non-serious events for both studies combined through December 31, 2004. Refer to the attached Table of Contents for specific details of tables included.

The required archival and review copies of this submission are being sent to the Central Document Room. In addition, an electronic copy is being sent to Dr. Lim.

The information in this submission is confidential and as such should be handled in accordance with the provisions established under 21 CFR 314.430.

If you have any questions regarding this correspondence, please contact me at (813) 866-1668 or by facsimile at (813) 975-7757 or by e-mail at [yelen\\_concepcion@bausch.com](mailto:yelen_concepcion@bausch.com).

Sincerely,



Yelen Concepcion  
Manager, Regulatory Affairs – Pharmaceuticals

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**Bausch & Lomb™**

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Tampa, FL 33637  
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February 23, 2005

Wiley Chambers, M.D., Deputy Director  
Division of Anti-Inflammatory, Analgesic, and  
Ophthalmologic Drug Products (HFD-550)  
Center for Drug Evaluation and Research  
FOOD AND DRUG ADMINISTRATION  
Attention: Central Document Room  
9201 Corporate Blvd  
Rockville, MD 20850

**RE: NDA 21-737  
Fluocinolone Acetonide Intravitreal Implant (Retisert™)  
Response to FDA Statistical Data Question of 02/15/05**

Dear Dr. Chambers:

Reference is made to our pending Fast Track NDA 21-737 for the above referenced drug product for the treatment of noninfectious uveitis affecting the posterior segment of the eye. The complete NDA was filed on October 7, 2004.

This amendment to the NDA provides additional information requested via e-mail by Statistical Reviewer Dr. Rahman on 02/15/05. In response to the request, we are providing two additional transport datasets for Clinical Study BLP 415-001 that were not included in the original NDA. Datasets are being provided on CD. See attached complete response for details (Attachment I).

The required archival and review copies of this submission are being sent to the Central Document Room. Copies of the CD with the additional datasets are included in the archival copy and in a desk copy to Project Manager Raphael Rodriguez for distribution to Dr. Rahman.

The information in this submission is confidential and as such should be handled in accordance with the provisions established under 21 CFR 314.430.

If you have any questions regarding this correspondence, please contact me at (813) 866-2568 or by facsimile at (813) 975-7757 or by e-mail at yelen\_concepcion@bausch.com.

Sincerely,



Yelen Concepcion  
Manager, Regulatory Affairs – Pharmaceuticals


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February 23, 2005

Wiley Chambers, M.D., Deputy Director  
Division of Anti-Inflammatory, Analgesic, and  
Ophthalmologic Drug Products (HFD-550)  
Center for Drug Evaluation and Research  
FOOD AND DRUG ADMINISTRATION  
Attention: Central Document Room  
9201 Corporate Blvd  
Rockville, MD 20850

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FEB 25 2005

MEGA / CDER

N-000(BM)  
ORIG AMENDMENT

**RE: NDA 21-737**  
**Fluocinolone Acetonide Intravitreal Implant (Retisert™)**  
**Additional CRF's per FDA Request: BLP 415-001 and BLP 415-004**

Dear Dr. Chambers:

Reference is made to our pending Fast Track NDA 21-737 for the above referenced drug product for the treatment of noninfectious uveitis affecting the posterior segment of the eye. The complete NDA was filed on October 7, 2004.

In response to a request received from Clinical Reviewer Dr. Lim on 02/02/05, we are providing additional CRF's from randomly selected patients participating in our pivotal clinical studies, BLP 415-001 and BLP 415-004 as follows:

- 1) Five (5) random patients from each of the pivotal studies who did not experience a uveitis recurrence in the 34-week period prior to implantation and five (5) random patients from each study who did experience a uveitis recurrence in the 34 week period prior to implantation.
- 2) Five (5) random patients from each of the pivotal studies who did not experience a uveitis recurrence in the post 34-week period following implantation and five (5) random patients from each study who did experience a uveitis recurrence in the post 34-week period.

The above referenced CRF's are provided on CD as agreed upon with Dr. Lim. Provided with this submission is a table of contents identifying patient ID and corresponding study number for all individual patient CRF's provided (see Attachment 1).

The required archival and review copies of this submission are being sent to the Central Document Room. Copies of the CD with CRF's are included in the archival copy and in a desk copy to Project Manager Raphael Rodriguez for distribution to Dr. Lim.

The information in this submission is confidential and as such should be handled in accordance with the provisions established under 21 CFR 314.430.

If you have any questions regarding this correspondence, please contact me at (813) 866-2568 or by facsimile at (813) 975-7757 or by e-mail at [yelen\\_concepcion@bausch.com](mailto:yelen_concepcion@bausch.com).

Sincerely,



Yelen Concepcion  
Manager, Regulatory Affairs – Pharmaceuticals

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February 11, 2005

Wiley Chambers, M.D., Deputy Director  
Division of Anti-Inflammatory, Analgesic, and  
Ophthalmologic Drug Products (HFD-550)  
Center for Drug Evaluation and Research  
FOOD AND DRUG ADMINISTRATION  
Attention: Central Document Room  
9201 Corporate Blvd  
Rockville, MD 20850

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FEB 15 2005

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ORIG AMENDMENT

**RE: NDA 21-737**  
**Fluocinolone Acetonide Intravitreal Implant (Retisert™)**  
**Visual Acuity Changes from Baseline to 34 Weeks: BLP 415-001 and BLP**  
**415-004**

Dear Dr. Chambers:

Reference is made to our pending Fast Track NDA 21-737 for the above referenced drug product for the treatment of noninfectious uveitis affecting the posterior segment of the eye. The complete NDA was filed on October 7, 2004.

In response to a request received via e-mail from Clinical Reviewer Dr. Lim on 02/08/05, we are providing tables that summarize visual acuity changes in the intent-to-treat population of pivotal studies, BLP 415-001 and BLP 415-004. The tables present line changes in visual acuity from baseline to 34 weeks post implantation in the format requested by the reviewer (see Attachments I and II).

The required archival and review copies of this submission are being sent to the Central Document Room. In addition, an electronic copy is being sent to Dr. Lim.

The information in this submission is confidential and as such should be handled in accordance with the provisions established under 21 CFR 314.430.

If you have any questions regarding this correspondence, please contact me at (813) 866-2568 or by facsimile at (813) 975-7757 or by e-mail at [yelen\\_concepcion@bausch.com](mailto:yelen_concepcion@bausch.com).

Sincerely,



Yelen Concepcion  
Manager, Regulatory Affairs – Pharmaceuticals

ORIGINAL



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February 09, 2005

Wiley Chambers, M.D., Deputy Director  
Division of Anti-Inflammatory, Analgesic, and  
Ophthalmologic Drug Products (HFD-550)  
Center for Drug Evaluation and Research  
FOOD AND DRUG ADMINISTRATION  
Attention: Central Document Room  
9201 Corporate Blvd  
Rockville, MD 20850

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FEB 10 2005

ORIG AMENDMENT MEGA / CDER  
N000(BN)

**RE: NDA 21-737**  
**Fluocinolone Acetonide Intravitreal Implant (Retisert™)**  
**34-Week Non-Serious AE Incidence Summary Tables: BLP 415-001 and BLP 415-004**

Dear Dr. Chambers:

Reference is made to our pending Fast Track NDA 21-737 for the above referenced drug product for the treatment of noninfectious uveitis affecting the posterior segment of the eye. The complete NDA was filed on October 7, 2004.

In response to a request from Clinical Reviewer Dr. Lim, we are amending the above referenced NDA to provide separate incidence summary tables for the non-serious adverse events (AE's) from our two pivotal clinical studies, BLP 415-001 and BLP 415-004. The original NDA contained AE incidence summary tables that combined the serious and non-serious events through 34 weeks post implantation. Consequently, on 02/03/05, Dr. Lim asked to see the non-serious and serious AE's in separate summary tables for the pivotal studies.

This submission provides, for each of the pivotal studies, the non-serious AE's through 34 weeks as separate incidence summary tables which include ocular non-serious AE's (study eye and fellow eye) and non-ocular non-serious AE's. Additionally, incidence summary tables of ocular (study eye and fellow eye) and non-ocular non-serious AE's are provided for both studies combined. Separate incidence summary tables for serious adverse events (SAE's) through 34 weeks were provided in the original NDA and are not reproduced in this submission.

The required archival and review copies of this submission are being sent to the Central Document Room. In addition, an electronic copy is being sent to Dr. Lim.

The information in this submission is confidential and as such should be handled in accordance with the provisions established under 21 CFR 314.430.

If you have any questions regarding this correspondence, please contact me at (813) 866-2568 or by facsimile at (813) 975-7757 or by e-mail at [yelen\\_concepcion@bausch.com](mailto:yelen_concepcion@bausch.com).

Sincerely,



Yelen Concepcion  
Manager, Regulatory Affairs – Pharmaceuticals

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February 07, 2005

Wiley Chambers, M.D., Deputy Director  
Division of Anti-Inflammatory, Analgesic, and  
Ophthalmologic Drug Products (HFD-550)  
Center for Drug Evaluation and Research  
FOOD AND DRUG ADMINISTRATION  
Attention: Central Document Room  
9201 Corporate Blvd  
Rockville, MD 20850

**RE: NDA 21-737**  
**Fluocinolone Acetonide Intravitreal Implant (Retisert™)**  
**4-Month Safety Update**

Dear Dr. Chambers:

Reference is made to our pending Fast Track NDA 21-737 for the above referenced drug product for the treatment of noninfectious uveitis affecting the posterior segment of the eye. The complete NDA was filed on October 7, 2004.

In accordance with 21 CFR 314.50(d)(5)(vi)(b), Bausch & Lomb (B&L) is hereby submitting the 4-Month Safety Update for the above referenced pending application. The following information is provided with this safety update:

- Updated Section 2.7 Clinical Summary
- Updated Report on the Analysis of Explanted Retisert from Clinical Studies
- Case Report Forms (on CD)
- Updated Package Insert

The updated 2.7 Clinical Summary contains new safety and efficacy information from our ongoing clinical studies with the Retisert implant. Specifically, we are providing updated adverse event and exposure information from all clinical studies through June 30, 2004 and updated SAE Listings and Narratives through September 30, 2004. In addition, based on a request from the Clinical Reviewer, Dr. Lim, on December 17, 2004 for a listing of adverse events through January 2005, we are including an appendix in the updated Clinical Summary that contains adverse event information up to January 1, 2005 (See Section 2.7.4.7.7 Supplemental AE Presentation, volume 9). To facilitate review of the data provided, we are including a summary of the cut-off dates for the various AE tables provided in this update (see attachment labeled "Cut-off Dates Summary", volume 1).

Note that AE summary tables in this submission consist of non-serious and serious adverse events. Separate summary tables are also provided in this submission that include just serious AE's. To comply with a request from Clinical Reviewer Dr. Lim, we will be providing incidence summary tables that include just the non-serious AE's for the two pivotal Phase III uveitis trials, BLP 415-001 and BLP 415-004. These tables will be provided in a separate submission following this update.

We have also updated Section 2.7.3 Summary of Clinical Efficacy with 1-year efficacy data from the two pivotal Phase III uveitis trials, BLP 415-001 and BLP 415-004. One year clinical study reports for the pivotal trials will be available upon request.

In addition, the annotated package insert has been updated to reflect new safety and efficacy information per the updated Clinical Summary. Case Report Forms for this update are being submitted electronically on CD as previously agreed upon with the FDA.

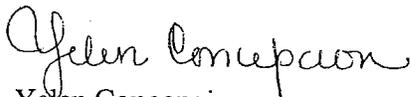
This submission consists of nine volumes. For more details on the location of the information provided, please see the Overall Table of Contents.

The required archival and review copies of this submission are being sent to the Central Document Room. In addition, a desk copy is being sent to Project Manager Raphael Rodriguez. Volume 1 of the archival copy contains a CD with the updated package insert and two CD's with CRF's. The desk copy being sent to Raphael Rodriguez also contains copies of these CD's.

The information in this submission is confidential and as such should be handled in accordance with the provisions established under 21 CFR 314.430.

If you have any questions regarding this application, please contact me at (813) 866-2568 or by facsimile at (813) 975-7757 or by email at [Yelen\\_concepcion@bausch.com](mailto:Yelen_concepcion@bausch.com).

Sincerely,



Yelen Concepcion  
Manager, Regulatory Affairs – Pharmaceuticals

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February 3, 2005

Wiley Chambers, M.D., Deputy Director  
Division of Anti-Inflammatory, Analgesic, and  
Ophthalmologic Drug Products (HFD-550)  
Center for Drug Evaluation and Research  
FOOD AND DRUG ADMINISTRATION  
Attention: Central Document Room  
9201 Corporate Blvd  
Rockville, MD 20850

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FEB 04 2005

ORIG AMENDMENT MEGA / CDER  
N-000(BM)

**RE: NDA 21-737**  
**Fluocinolone Acetonide Intravitreal Implant (Retisert™)**  
**Electronic Copies of CRF's for BLP 415-001 and BLP 415-004**

Dear Dr. Chambers:

Reference is made to our pending Fast Track NDA 21-737 for the above referenced drug product for the treatment of noninfectious uveitis affecting the posterior segment of the eye. The complete NDA was filed on October 7, 2004.

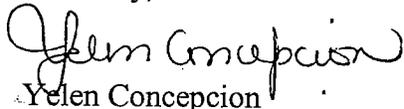
Through this correspondence, we are providing electronic copies of the Case Report Forms (CRF's) for the two pivotal studies, BLP 415-001 and BLP 415-004, to facilitate review of this data by the clinical reviewer. Hard copies of these CRF's were provided to FDA in the original NDA's archival copy (Module 5, Section 5.3.7) on October 7, 2004. The enclosed CD provides each individual patient CRF as a discreet PDF file indentified by Patient ID number and separated by study. Also provided with this submission are two tables that identify the CRF's included per study (these tables were submitted in the original NDA accompanying the hard copy CRF's). Each electronic CRF provided has been re-organized in a manner that is more amenable for review.

The required archival and review copies of this submission are being sent to the Central Document Room. In addition, a desk copy is being sent to Project Manager Raphael Rodriguez containing a CD for distribution to the clinical reviewer. The archival copy also contains a copy of the CD.

The information in this submission is confidential and as such should be handled in accordance with the provisions established under 21 CFR 314.430.

Please contact the undersigned should you have any questions and or comments regarding this correspondence.

Sincerely,



Yelen Concepcion

Manager, Regulatory Affairs – Pharmaceuticals

Telephone: (813) 866-2568

Facsimile: (813) 975-7757

e-mail: [yelen\\_concepcion@bausch.com](mailto:yelen_concepcion@bausch.com)

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January 31, 2005

N-000(BC)

Wiley Chambers, M.D., Deputy Director  
Division of Anti-Inflammatory, Analgesic, and  
Ophthalmologic Drug Products (HFD-550)  
Center for Drug Evaluation and Research  
FOOD AND DRUG ADMINISTRATION  
Attention: Central Document Room  
9201 Corporate Blvd  
Rockville, MD 20850

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FEB 02 2005

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ORIG AMENDMENT

**RE: NDA 21-737 - Fluocinolone Acetonide Intravitreal Implant (Retisert™)  
Response to CMC Questions of 12/15/04: Part 2  
CFR 5251, Rev C: 39-Week Stability Report  
Updated Methods Validation Package**

Dear Dr. Chambers:

Reference is made to our pending Fast Track NDA 21-737 for the above referenced drug product for the treatment of noninfectious uveitis affecting the posterior segment of the eye. The complete NDA was filed on October 7, 2004.

This NDA amendment completes our response to a list of CMC questions dated 12/13/04 and received via facsimile on 12/15/04 from Chemistry Reviewer Dr. Su Tso. Responses to questions from the list not provided in this submission were previously submitted to FDA on 01/14/05. Changes to methods and validations in response to issues raised by Dr. Tso necessitated an update to the Methods Validation Package, which is also included herein. To facilitate review, a table is provided with FDA questions reproduced in bold and/or italics, followed by our responses (unbolded).

Also included in this amendment are 39-week (9-months) stability results for the three site-specific stability batches manufactured in B&L, Ireland. Refer to Appendix 9 for a copy of the stability report.

The required archival and review copies of this submission are being sent to the Central Document Room. In addition, a desk copy is being sent to Project Manager Raphael Rodriguez for distribution to Dr. Tso.

In accordance with 21 CFR 314.60(c), we certify that a true copy of the information contained in this amendment has been forwarded to FDA's Orlando District Office.

ORIGINAL



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January 14, 2005

Wiley Chambers, M.D., Deputy Director  
Division of Anti-Inflammatory, Analgesic, and  
Ophthalmologic Drug Products (HFD-550)  
Center for Drug Evaluation and Research  
FOOD AND DRUG ADMINISTRATION  
Attention: Central Document Room  
9201 Corporate Blvd  
Rockville, MD 20850

**RE: NDA 21-737  
Fluocinolone Acetonide Intravitreal Implant (Retisert™)  
Response to CMC Questions of 12/13/04**

Dear Dr. Chambers:

Reference is made to our pending Fast Track NDA 21-737 for the above referenced drug product for the treatment of noninfectious uveitis affecting the posterior segment of the eye. The complete NDA was filed on October 7, 2004.

We are amending the above referenced NDA in response to a list of CMC questions dated 12/13/04 and received via facsimile on 12/15/04 from Chemistry Reviewer Dr. Su Tso. The CMC information requested by Dr. Tso is provided herein. To facilitate review, FDA questions are reproduced in bold and italics, followed by our response (unbolded).

We hope the information provided in this amendment adequately responds to the CMC issues raised by Dr. Tso. As indicated in the enclosed responses, methods and validations for drug substance and drug product are being updated as requested. Updated documentation will be provided by January 31<sup>st</sup>.

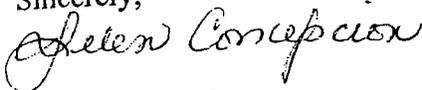
The required archival and review copy of this submission are being sent to the Central Document Room. In addition, a desk copy is being sent to Project Manager Raphael Rodriguez for distribution to Dr. Tso.

In accordance with 21 CFR 314.60(c), we certify that a true copy of the information contained in this amendment has been forwarded to FDA's Orlando District Office.

The information in this submission is confidential and as such should be handled in accordance with the provisions established under 21 CFR 314.430.

Please contact the undersigned should you have any questions and or comments regarding this correspondence.

Sincerely,



Yelen Concepcion

Manager, Regulatory Affairs – Pharmaceuticals

Telephone: (813) 866-2568

Facsimile: (813) 975-7757

e-mail: [yelen\\_concepcion@bausch.com](mailto:yelen_concepcion@bausch.com)

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**FILING COMMUNICATION**

NDA 21-737

Bausch & Lomb, Inc.  
Attention: Yelen Concepcion  
Manager, Regulatory Affairs  
8500 Hidden River Parkway  
Tampa, FL 33637

Dear Ms. Concepcion:

Please refer to your New Drug Application (NDA) submission of October 7, 2004, for Retisert (fluocinolone acetonide intravitreal implant) 0.59 mg. This submission, accepted under the Continuous Marketing Application (CMA)-Pilot 1 program, contained the reviewable units for Clinical and Chemistry portions of your NDA.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application was filed under section 505(b) of the Act on December 7, 2004, in accordance with 21 CFR 314.101(a).

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

If you have any questions, call Raphael R. Rodriguez, Regulatory Project Manager, at (301) 827-2090.

Sincerely,

*{See appended electronic signature page}*

Carmen DeBellas, R.Ph.  
Chief, Project Management Staff  
Division of Anti-Inflammatory, Analgesic,  
and Ophthalmic Drug Products, HFD-550  
Office of Drug Evaluation V  
Center for Drug Evaluation and Research

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

-----  
Carmen DeBellas  
12/6/04 09:09:11 AM

**Bausch & Lomb**

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Tampa, FL 33637  
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November 17, 2004

Wiley Chambers, M.D., Deputy Director  
Division of Anti-Inflammatory, Analgesic, and  
Ophthalmologic Drug Products (HFD-550)  
Center for Drug Evaluation and Research  
FOOD AND DRUG ADMINISTRATION  
Attention: Central Document Room  
9201 Corporate Blvd  
Rockville, MD 20850

*N-000(BM)*

ORIG AMENDMENT

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NOV 18 2004

MEGA/CDER

**RE: NDA 21-737**  
**Fluocinolone Acetonide Intravitreal Implant (Retisert™)**  
**List of Investigators and Enrollment Numbers**

Dear Dr. Chambers:

Reference is made to our pending Fast Track NDA 21-737 for the above referenced drug product for the treatment of noninfectious uveitis affecting the posterior segment of the eye. The complete NDA was filed on October 7, 2004.

In response to a request from Dianne Tesch, Consumer Safety Officer, received on November 12, we are providing a list of investigators for all the clinical studies included in the above referenced NDA. As requested, the list includes the name of each principal investigator, site address, and number of enrolled subjects. This information has also been e-mailed to Dianne Tesch.

The required archival and review copies of this submission are being sent to the Central Document Room. In addition, desk copies are being sent to Project Manager Raphael Rodriguez and Dianne Tesch.

The information in this submission is confidential and as such should be handled in accordance with the provisions established under 21 CFR 314.430.

Sincerely,



Yelen Concepcion  
Manager, Regulatory Affairs – Pharmaceuticals

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November 16, 2004

Wiley Chambers, M.D., Deputy Director  
Division of Anti-Inflammatory, Analgesic, and  
Ophthalmologic Drug Products (HFD-550)  
Center for Drug Evaluation and Research  
FOOD AND DRUG ADMINISTRATION  
Attention: Central Document Room  
9201 Corporate Blvd  
Rockville, MD 20850

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*N-000(BM)*

ORIG AMENDMENT

**RE: NDA 21-737**  
**Fluocinolone Acetonide Intravitreal Implant (Retisert™)**  
**Electronic Copies of Clinical Study Reports**

Dear Dr. Chambers:

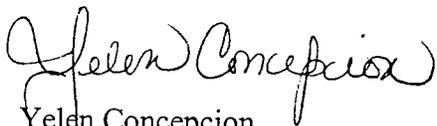
Reference is made to our pending Fast Track NDA 21-737 for the above referenced drug product for the treatment of noninfectious uveitis affecting the posterior segment of the eye. The complete NDA was filed on October 7, 2004.

In response to a request from Dr. Rahman, statistical reviewer, received on November 16<sup>th</sup>, enclosed please find a CD with the copies of the electronic files for the safety and efficacy study reports identified in Section 5.3.5 of the above-referenced NDA.

The required archival copy of this submission is being sent to the Central Document Room. In addition, a desk copy is being sent to Project Manager Raphael Rodriguez containing the CD for distribution to Dr. Rahman.

The information in this submission is confidential and as such should be handled in accordance with the provisions established under 21 CFR 314.430.

Sincerely,



Yelen Concepcion  
Manager, Regulatory Affairs – Pharmaceuticals

ORIGINAL

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November 11, 2004

Wiley Chambers, M.D., Deputy Director  
Division of Anti-Inflammatory, Analgesic, and  
Ophthalmologic Drug Products (HFD-550)  
Center for Drug Evaluation and Research  
FOOD AND DRUG ADMINISTRATION  
Attention: Central Document Room  
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Rockville, MD 20850

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*N-000(S4)*

ORIG AMENDMENT

**RE: NDA 21-737**  
**Fluocinolone Acetonide Intravitreal Implant (Retisert™)**  
**Proposal for the 4-Month Safety Update**

Dear Dr. Chambers:

Reference is made to our pending Fast Track NDA 21-737 for the above referenced drug product for the treatment of noninfectious uveitis affecting the posterior segment of the eye. The complete NDA was filed on October 7, 2004.

In accordance with 21 CFR 314.50(d)(5)(vi)(b), Bausch & Lomb (B&L) is required to update the pending application with new safety information 4 months after the initial submission. In addition, applicants are encouraged to consult with FDA regarding details of the organization and content of the required update report.

B&L proposes to submit the 4-month safety update as an updated Module 2, Section 2.7 Clinical Summary. We will update relevant sections of the Clinical Summary with new information from clinical studies, animal studies and/or the literature. Specifically, we will provide updated adverse event and exposure information from all clinical studies through June 30, 2004 and updated SAE Listings and Narratives through September 30, 2004 as appendices to Section 2.7. We will also update Section 2.7.3 Summary of Clinical Efficacy with 1-year efficacy data from our two pivotal Phase III posterior uveitis trials, BLP 415-001 and BLP 415-004.

As agreed with FDA at the Pre-NDA Meeting, Case Report Forms for all patients who died or discontinued from a study were provided in the original NDA submission. For the original NDA, Case Report Forms constituted 127 volumes. For the 4-month safety update, we propose to submit "Case Histories" in lieu of the Case Report Forms for patients who died or withdrew from the studies. Each "Case History" is a tabulation of the information contained in an individual patient's Case Report Form. A sample "Case History" tabulation is attached for your review.

DUPLICATE

In addition to an updated Section 2.7 Clinical Summary and "Case Histories," we will also provide a revised draft package insert updated with new safety and efficacy information.

We ask for your concurrence with our proposal for the 4-month safety update report, due to FDA on February 7, 2005, especially in regard to the submission of "Case Histories" in lieu of Case Report Forms. For planning purposes, we would appreciate receiving a response by November 24, 2004.

The required archival and review copy of this submission are being sent to the Central Document Room. In addition, a desk copy is being sent to Project Manager Raphael Rodriguez.

The information in this submission is confidential and as such should be handled in accordance with the provisions established under 21 CFR 314.430.

Sincerely,



Yelen Concepcion  
Manager, Regulatory Affairs – Pharmaceuticals

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

## DISCIPLINE REVIEW LETTER

NDA 21-737

Bausch & Lomb, Inc.  
Attention: Yelen Concepcion  
Manager, Regulatory Affairs  
8500 Hidden River Parkway  
Tampa, FL 33637

Dear Ms. Concepcion:

Please refer to your New Drug Application (NDA) submission of May 28, 2004, for Retisert (fluocinolone acetonide intravitreal implant) 0.59 mg. This submission, accepted under the Continuous Marketing Application (CMA)-Pilot 1 program, contained the reviewable unit for the Nonclinical Pharmacology and Toxicology portions of your NDA.

We have completed our review of this reviewable unit and have not identified any potential deficiencies at this time.

This letter is being provided to you in conformance with the guidance "Continuous Marketing Applications: Pilot 1 – Reviewable Units for Fast Track Products under PDUFA" and does not reflect a final decision on the information reviewed. Issues may be added, expanded upon, or modified as we review the Clinical and Chemistry sections.

Upon receipt and review of your 120-day Safety Update, in coordination with the review of the remainder of the NDA, we will work with you on the proposed labeling for this product.

If you have any questions, call Raphael R. Rodriguez, Regulatory Project Manager, at (301) 827-2090.

Sincerely,

*{See appended electronic signature page}*

Josie Yang, DVM, Ph.D.  
Pharmacology/Toxicology Team Leader for the  
Division of Anti-Inflammatory, Analgesic, and  
Ophthalmic Drug Products, HFD-550  
Office of Drug Evaluation V  
Center for Drug Evaluation and Research

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

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Josie Yang  
11/4/04 01:12:26 PM

**Bausch & Lomb™**

8500 Hidden River Parkway  
Tampa, FL 33637  
813.975.7700  
www.bausch.com

November 2, 2004

Wiley Chambers, M.D., Deputy Director  
Division of Anti-Inflammatory, Analgesic, and  
Ophthalmologic Drug Products (HFD-550)  
Center for Drug Evaluation and Research  
FOOD AND DRUG ADMINISTRATION  
Attention: Central Document Room  
9201 Corporate Blvd  
Rockville, MD 20850

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NOV 04 2004 NOV 03 2004

MEGA / CDER CDR / CDER

RE: **NDA 21-737**  
**Fluocinolone Acetonide Intravitreal Implant (Retisert™)**  
**Packaged Drug Product Sample**

N1-000(BC)  
ORIG AMENDMENT

Dear Dr. Chambers:

In response to a request from Chemistry Reviewer Dr. Su Tso, we are providing a sample of the Fluocinolone Acetonide Intravitreal Implant (Retisert™), subject of the above referenced pending New Drug Application.

Dr. Tso requested a sample of the drug product in its proposed commercial packaging configuration on October 20, 2004. Provided with this correspondence is a sample of the 0.59 mg Retisert™ implant packaged in a mock-up of the proposed commercial container closure configuration and graphic artwork as described in the NDA (Module 1, Section 1.16 and Module 3, Section 3.2.P.7). Note the following differences between the proposed commercial package and the mock-up provided:

- *Carton:* The graphic artwork on the commercial carton will have a more premium look due to the use of green foil for the chevron accent (narrow green "checkmark" at the top of the blue base) and metallized blue ink for the blue base on the primary display (front) panel.
- *Package Insert:* The package insert text is draft only. The mock-up is printed on a much thicker paper than what will be used for commercial printing. The paper proposed for commercial printing will retain the fold pattern better and lie flatter in the carton.
- *Foil and Tyvek Pouch:* The pouches are provided unsealed to allow the reviewer easy access to the implant without damaging the package.

ORIGINAL

The required archival and review copies of this submission are being sent to the Central Document Room. In addition, a desk copy is being sent to Project Manager Raphael Rodriguez. The sample described above is included with the desk copy being sent to Raphael Rodriguez for distribution to Dr. Tso.

The information in this submission is confidential and as such should be handled in accordance with the provisions established under 21 CFR 314.430.

Sincerely,

*Helen Concepcion*

Helen Concepcion  
Manager, Regulatory Affairs – Pharmaceuticals

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October 07, 2004

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OCT 12 2004

MEGA/CDER

Wiley Chambers, M.D., Deputy Director  
Division of Anti-Inflammatory, Analgesic, and  
Ophthalmologic Drug Products (HFD-550)  
Center for Drug Evaluation and Research  
FOOD AND DRUG ADMINISTRATION  
Attention: Central Document Room  
9201 Corporate Blvd  
Rockville, MD 20850

**RE: NDA 21-737  
Fluocinolone Acetonide Intravitreal Implant (Retisert™)  
Submission of Original CMC and Clinical Reviewable Unit**

Dear Dr. Chambers:

Reference is made to IND 60,000 for the Fluocinolone Acetonide Intravitreal Implant (FAII). Reference is also made to Fast Track designation granted by FDA on 04/28/00, Orphan Drug designation granted on 08/03/00, and CMA Pilot 1 Program approval granted on 01/26/04 to Bausch & Lomb for the FAII for the treatment of non-infectious posterior uveitis.

Pursuant to Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, and the CMA Pilot 1 Program under PDUFA III, Bausch & Lomb is hereby submitting the second and final reviewable unit of a New Drug Application for the above referenced Fast Track product for the localized treatment of non-infectious posterior uveitis.

The first reviewable unit (RU1) consisted of a complete Preclinical Section in the format of the Common Technical Document (CTD) and was submitted on May 28, 2004. At this time, a second and final reviewable unit (RU2) consisting of a complete CMC and Clinical Section in CTD format is being submitted. This second reviewable unit completes the NDA. As requested by FDA at the Pre-NDA Meeting held on May 10, 2004, complete Modules 1 and 2 are being submitted (i.e., sections of Modules 1 and 2 previously submitted with the first reviewable unit are being re-submitted with this unit). Module 4 (Nonclinical Study Reports) is not being re-submitted.

This submission consists of 238 volumes. Each module is bound in separate volumes and all documents are separated by tab identifiers. The required archival copy (blue-jacketed) and relevant technical review copies for Module 3 and Module 5 are being sent to the Central Document Room. Complete archival and technical review copies of Modules 1 and 2 are also being sent to the Central Document Room. In addition, as requested by

FDA at the May 10, 2004 Pre-NDA meeting, six (6) desk copies of Modules 1 and 2 are also being sent to the attention of DAAODP Project Manager Raphael Rodriguez for distribution as needed.

- Module 1 (1 volume): Archival (blue-jacketed), technical review copies (tan, red, green, orange, and white-jacketed), six (6) desk copies.
- Module 2 (2 volumes): Archival (blue-jacketed), technical review copies (tan, red, green, orange, and white-jacketed), six (6) desk copies.
- Module 3 (12 volumes): Archival (blue-jacketed), and technical review copies (red and white-jacketed).
- Module 4: Previously submitted with RUI and not being resubmitted.
- Module 5 (223 volumes): Archival (blue-jacketed), and technical review copies (tan, green, and orange-jacketed\*).

Included in the archival copy of Module 1, Volume 2.1, are CD-ROMs containing SAS datasets for the following clinical studies: BLP 415-001, BLP 415-004, FL-002, and FL-005. As agreed at the pre-NDA meeting, the SAS dataset files are being provided electronically, in lieu of Appendix 16.4 of the clinical reports for these studies. Additionally included in Module 1, Volume 2.1 of the archival copy is a CD-ROM containing the proposed, draft package insert text in Microsoft Word format. Case Report Forms are only included in the archival copy of Module 5 (Volumes 1.97 –1.222).

The proposed trade name, Retisert™, was previously submitted under IND 60,000 on 09/25/00. The FDA Division in charge of trade name reviews at that time, OPDRA (Office of Post-marketing Drug Risk Assessment), conducted a review to determine the potential for confusion of the Retisert™ name with approved proprietary and generic names as well as pending names. On September 2001, OPDRA's recommendation was that it did not object to the use of the proprietary name Retisert™, but indicated that the name would need to be re-evaluated approximately 90 days prior to the expected approval of the NDA. At this time, B&L requests a re-review of the Retisert™ trade name by DMETS (Office of Drug Safety, Division of Medication Errors and Technical Support).

In accordance with 21 CFR 314.50(d)(1)(v), we certify that a true copy of the information contained in Modules 1, 2, and 3 of this application has been forwarded to FDA's Orlando District Office.

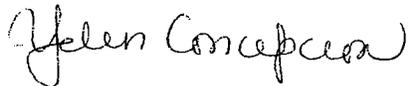
The information in this submission is confidential and as such should be handled in accordance with the provisions established under 21 CFR 314.430.

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\* The orange-jacketed, PK technical review copy, only contains Sections 5.1, 5.2, 5.3.1, 5.3.2, 5.3.3, and Section 5.3.5.1.1 BLP 415-001 [body of the report and Appendix 16.2.5 only].

If you have any questions regarding this application, please contact me at (813) 866-2568 or by facsimile at (813) 975-7757 or by email at Yelen\_concepcion@bausch.com. Additionally, please direct all correspondence on this application to my attention

Sincerely,

A handwritten signature in cursive script that reads "Yelen Concepcion".

Yelen Concepcion  
Manager, Regulatory Affairs – Pharmaceuticals

Appears This Way  
On Original

**Bausch & Lomb™**

8500 Hidden River Parkway  
Tampa, FL 33637  
813.975.7700  
www.bausch.com

October 07, 2004

Ms. Emma Singleton  
District Director  
Orlando district Office  
U.S. Food and Drug Administration  
555 Winderley Place, Suite 200  
Maitland, FL 32751

**RE: NDA No. 21-737  
Fluocinolone Acetonide Intravitreal Implant (Retisert™)  
New Drug Application**

Dear Ms. Singleton:

In accordance with 21 CFR 314.50 (d)(1)(v), we certify that this correspondence is a true copy of the information described in 21 CFR 314.50(l)(3) and contained in the above referenced new drug application as modules 1, 2 and 3:

- Module 1: Administrative and Prescribing Information
- Module 2: CTD Summaries
- Module 3: Quality (chemistry, manufacturing, and controls)

The original correspondence was submitted to the Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products.

The information contained in this application is confidential and as such should be handled in accordance with the provisions established in 21 CFR 314.430.

If you have any questions regarding this information, please contact me at:

Phone (813) 866-2568  
Fax (813) 975-7757  
e-mail yelen\_concepcion@bausch.com

Sincerely,

*Yelen Concepcion*

Yelen Concepcion  
Manager, Regulatory Affairs



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 60,000

Bausch & Lomb, Inc.  
Attention: Yelen Concepcion  
Manager, Regulatory Affairs  
8500 Hidden River Parkway  
Tampa, Florida 33637

Dear Ms. Concepcion:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fluocinolone Acetonide Intravitreal Implant.

We also refer to the Pre-NDA Meeting between representatives of your firm and the FDA on May 10, 2004.

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 Michael Puglisi, Project Manager, at (301) 827-2090.

Sincerely,

*{See appended electronic signature page}*

Wiley A. Chambers, M.D.  
Deputy Director  
Division of Anti-Inflammatory, Analgesic  
and Ophthalmic Drug Products, HFD-550  
Office of Drug Evaluation V  
Center for Drug Evaluation and Research

Enclosure



**MEMORANDUM OF MEETING MINUTES**

**MEETING DATE:** May 10, 2004  
**START TIME:** 2:30 pm  
**LOCATION:** 9201 Corporate Boulevard

**APPLICATION (DRUG):** IND 60,000  
Fluocinolone Acetonide Intravitreal Implant

**SPONSOR:** Bausch & Lomb, Inc.

**TYPE OF MEETING:** Pre-NDA

**MEETING CHAIR:** Wiley A. Chambers, MD

**MEETING RECORDER:** Michael Puglisi

**FDA PARTICIPANTS:**

Dennis Bashaw/ Clinical Pharmacology Team Leader  
William Boyd/ Clinical Team Leader  
Jonca Bull/ ODE 5 Director  
Wiley Chambers/ Deputy Division Director  
Conrad Chen/ Pharmacologist  
Carmen DeBellas/ Chief Project Manager  
Lori Gorski/ Project Manager  
Jennifer Harris/ Medical Officer  
Lucious Lim/ Medical Officer  
Stan Lin/ Statistics Team Leader  
Linda Ng/ Chemistry Team Leader  
Mike Puglisi/ Project Manager  
Terri Rumble/ Associate Director, Regulatory Affairs  
Su Tso/ Chemist  
Josie Yang/ Pharmacology/Toxicology Team Leader

**INDUSTRY PARTICIPANTS:**

Timothy Comstock/ Director, Scientific and Clinical Affairs  
Yelen Concepcion/ Manager, Regulatory Affairs  
Tom Crescuillo/ Director, Clinical Programs

Don Handley/ Director, Regulatory Affairs  
David Heiler/ Director, Analytical Chemistry

Brian Levy/ V.P., Preclinical and Clinical Affairs

**MEETING OBJECTIVE:**

To discuss the Sponsor's plans for their upcoming NDA submission of Fluocinolone Acetonide Intravitreal Implant for treatment of non infectious uveitis affecting the posterior segment of the eye.

**SUMMARY OF DISCUSSION:**

Responses to the Applicant's meeting questions were provided to them in an April 30, 2004, email. This meeting served to clarify those responses. The Applicant's questions and the Agency's responses are as follows:

**Preclinical**

Proposal 1:

A complete Table of Contents for the Preclinical Reviewable Unit (RU1) is provided herein (Section 5.0 Preclinical Plan). Does FDA have any comments or questions on the organization and contents for this reviewable unit?

*FDA Response: Acceptable*

**Clinical**

Proposal 2:

As previously communicated by FDA (September 27, 1999 FDA meeting, January 12, 2000 End of Phase II meeting, August 29, 2002 telephone contact), a minimum of 300 eyes is needed to support the safety of Retisert™ for the uveitis indication. For the two Phase III pivotal studies for uveitis, 415-001 and 415-004, we will have a total of approximately 213 patients with the 0.59 mg implant and 304 patients with the 2 mg implant. Assuming that the results of our Phase 3, controlled uveitis studies (BLP 415-001 and BLP 415-004) suggest that there is little or no difference in efficacy between the 0.59 mg and 2 mg Retisert™ in treating recurrent posterior uveitis, and the 0.59 mg implant becomes the proposed marketed product, and in order to meet the requirement of a minimum of 300 eyes for safety to support approval of the uveitis indication, the "Adverse Reactions" section of the label will be based on the adverse event profile observed with both the 0.59 mg and 2 mg dosage forms (all patients) from our two Phase III pivotal studies, 415-001 and 415-004. Does FDA concur with this approach?

***FDA Response:*** *Yes. Labeling would be expected to reflect the adverse event profile seen with both implants (but would not distinguish between the two unless both were marketed).*

Proposal 3:

The clinical module of the NDA will include safety and efficacy data on all patients from the two pivotal uveitis studies: 415-001 and 415-004 through 34 weeks post-implantation (the protocol-defined primary analysis timepoint). In addition, all serious adverse events received through February 15, 2004 (regardless of time lapsed since implantation) will be reported.

For all other studies, only exposure, disposition and safety data received by a predetermined cut-off date and serious adverse events received through February 15, 2004 will be presented. The exception will be \_\_\_\_\_ for which efficacy analyses will also be included because it has already been performed.

Refer to Table 1, "Tabulation of Clinical Studies," provided with this package (Section 5.0 Clinical Plan, page 41) which details cut-off dates for efficacy and safety data to be included in the original NDA per study. Does FDA have any comment or questions on the data and/or cut-off dates proposed for the initial NDA submission?

***FDA Response:*** *Bausch & Lomb should submit all safety and efficacy data currently available for the other studies at the time of the NDA submission.*

Proposal 4:

B&L will be preparing the 120-day safety update based on the filing date of the clinical reviewable unit, i.e., approximately December 29, 2004.

For the 120-day safety update, B&L proposes to provide safety and efficacy data through 1 year of patient exposure, AE's through June 30, 2004, and serious adverse events through September 30, 2004 for the two uveitis Phase III pivotal trials, 415-001 and 415-004. For all other studies, B&L proposes to present exposure, disposition, and safety data through June 30, 2004 and serious adverse events through September 30, 2004. Refer to Table 1, "Tabulation of Clinical Studies," (page 41) for details.

- a. With submission of 1 year efficacy data from the two Phase III trials in the 120-day safety update, would the agency accept this data for inclusion in the "Clinical Studies" section of the package insert?
- b. Given the clinical RU is filed August 31<sup>st</sup>, what would be the last date a clinical amendment would be acceptable without impacting the NDA review clock?

***FDA Response:*** *Final labeling is a review issue and would require a complete review of the submitted material.*

*Major amendments are strongly discouraged. The reviewable unit should be complete at the time of submission.*

Proposal 5:

Patient Data Listings: Section 16.4 of ICH E3, "Individual Patient Data Listing" (i.e., CRF Tabulations) are usually provided in paper form. These are "thematic" listings sorted by site, patient, and visit and include related information across patients, i.e. demographics, concomitant medications, dosing, efficacy, adverse events, vital signs, etc. These listings present the "raw" data as collected on the CRF and represents the contents of the database augmented by the addition of treatment codes. Section 16.4 of the clinical study reports for the pivotal studies, 415-001 and 415-004, is estimated to be 1000+ pages. Would FDA accept domain datasets (i.e., SAS transport files following the guidance document, "Providing Regulatory Submissions in Electronic Format- General Considerations," January 1999) in lieu of thematic data listings (hardcopy)?

*FDA Response: Acceptable.*

*Bausch & Lomb should submit the Case Report Forms for all discontinued subjects, regardless of cause.*

Proposal 6:

Data Files for the FDA: B&L proposes to provide FDA with analysis files that contain computed variables used in analyses, imputed missing data values such as missing or partial dates, and responders defined by visual review of case information, etc. We propose to supply these data files as SAS transport files accompanied by data definition files in PDF. Does FDA agree with this proposal?

*FDA Response: Acceptable.*

Proposal 7:

B&L will use MedDRA 4.1 coding for tabulations of adverse events. B&L requests guidance from FDA as to the most appropriate MedDRA hierarchy to be used for the "Adverse Reactions" section of the label, based on what has been used for ophthalmic products to date. If no recommendations/preferences exist, B&L proposes to present terms at the HLT level (Higher Level Terms). Does FDA agree?

*FDA Response: Our preference is a listing of verbatim terms and the associated Preferred Terms.*

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**Quality****Proposal 8:**

As with other approved implantable drug delivery systems, the designed release rate characteristics of Retisert™ will be important physician prescribing information. We anticipate that this information will be included in the "Description", "Clinical Pharmacology" and/or "Dosage and Administration" sections of the package insert. An example of potential text for the characterization of the Retisert™ implant to be included in the package insert follows:

*"Retisert™ is designed to release fluocinolone acetonide at a nominal initial rate of w µg/day, gradually decreasing over the first x months to a steady state between y-z µg/day over approximately 30 months."*

This statement will be based on the continuous, hydrated (wet) stability studies performed on Retisert™ implant batches. At the time of submission of the CMC module, 24 months hydrated stability data will be provided on three batches of implants manufactured at Control Delivery Systems, Inc. The 30 months timepoint on these three batches is in October 2004. We anticipate submitting the 30 months results at end-October/early-November. Will FDA accept these study results during the review of the NDA to support the labeling statement?

***FDA Response:*** *These study results will be acceptable only if the hydrated stability studies can be correlated to the drug release rate. Release rate study over x period should be provided. In addition, the absence or presence of the drug substance at 30 months should be assessed to support the statement.*

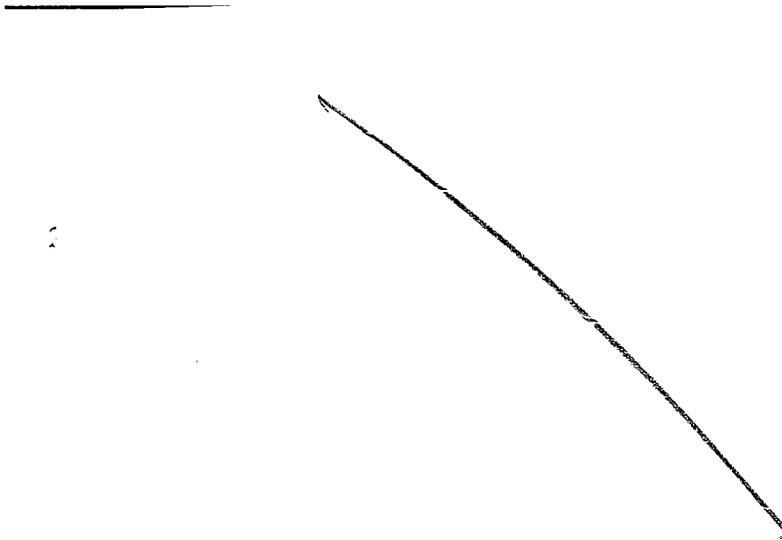
**Proposal 9:**

The historical development release rate specification limits for the 0.59 mg implant have been \_\_\_\_\_ based on the daily average of at least 12 implants over 4 days (i.e., the average of 12 implants for each of 4 days, then the average of the 4 days). Bausch & Lomb intends to move from 4 testing days to 1 testing day for the release rate average and data to support this change will be presented in the NDA.

***FDA Response:*** *The daily release rate profile of the X days should be submitted. A plot of release rate vs. time or total release vs. time should be provided over the proposed delivery time of 30 months. Release rate data should be determined during stability study. A daily average of implants up to 14 testing days should be collected. The acceptance criteria of the drug product specification will be deferred to the review of the NDA.*

Due to the nature of this product, Bausch & Lomb also intends to submit a more rigorous specification for release rate in the NDA and anticipates using a tiered specification approach

which would require additional testing should individual implant units lie outside a certain range. An example is shown below.



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*\*Same 12 units tested in Level 1.*

Does FDA have any comments at this time with a tiered approach for the release rate specification?

*FDA Response: Acceptable, but new implants should be used at each level of testing.*

Proposal 10:

Assuming that the results of our Phase III, controlled uveitis studies (BLP 415-001 and BLP 415-004) suggest that there is little or no difference in efficacy between the 0.59 mg and the 2 mg Retisert™ in treating recurrent posterior uveitis, and the 0.59 mg implant becomes the proposed marketed product, B&L proposes that relevant information and data on the 2 mg implant be provided in Section 3.2.P.2, "Pharmaceutical Development," and in Section 3.2.P.8, "Stability," only. Does FDA concur with this approach?

*FDA Response: Acceptable.*

Proposal 11:

The current packaging configuration for Retisert™ is as follows (described from inner to outer packaging):

- Primary Package for the product: polycarbonate case
- Secondary Package maintaining stability and sterility: ——— foil pouch
- Secondary Package: Tyvek pouch
- Secondary Package: paperboard carton
- Tertiary Package: corrugated shipper

For commercial product, Bausch & Lomb is proposing a change in carton style, size and potentially, material to facilitate easier handling by the end user and throughout the production process and to reduce carton and shipper waste. The current 10" L X 6.5" W X 7/8" D flip top carton design is cumbersome and difficult to handle. The Tyvek portion of the sealed Tyvek-Foil pouch combination can be easily folded over to facilitate loading into a smaller, user-friendly carton. As a secondary component, the function of the carton is only to provide structure for the final pack-off into shippers. It does not provide a primary barrier for the product. The sterilization procedure using the new carton configuration would be re-validated and submitted in the NDA (or in a supplement if done post-approval). Bausch & Lomb is proposing that a change in carton style, size and potentially, material, would not require additional stability studies prior to implementation. The first lot of commercially distributed product packaged with the new carton will be placed in stability. Does the agency concur?

*FDA Response: Yes.*

Proposal 12:

The Retisert™ implant is composed of a solid tablet encased in a silicone elastomer cup which is attached to a PVA suture tab. The dry drug product is packaged in a rigid, resealable polycarbonate case. The case is packaged within a sealed foil k ——— pouch. The implant does not come in direct contact with the inside of the foil pouch. ——— foil has excellent, well-established barrier properties. For commercial product, B&L plans to replace the current pre-printed foil pouches with an adhesive label applied to unprinted foil pouches. The adhesive label will contain all the labeling text previously pre-printed on the foil. Due to the nature of the dosage form and since the implants do not come in direct contact with the inside of the foil pouch, B&L proposes that a change to adhesive labels for the foil pouch would not require additional stability studies and/or extraction studies prior to implementation. Functional studies ( ) to ensure the integrity of the foil pouch with the adhesive label will be carried out. The first lot of product packaged in a foil pouch with adhesive label will be placed on stability. Does the agency concur?

*FDA Response: Acceptable.*

**Chemistry**

**Proposal 13:**

In addition to supportive stability data from representative clinical batches, the original NDA will include 24 months of long-term and accelerated stability data from three primary R&D stability batches manufactured at representative of lots used in preclinical and clinical studies. These lots are of production scale and are packaged in the container closure system proposed for marketing. The manufacturing process used at was subsequently transferred to B&L's manufacturing site at Waterford, Ireland, which is now the intended sole commercial manufacturing site. To support Waterford as the commercial manufacturing site and in accordance with the recommendations in FDA's draft stability guidance ("Stability Testing of Drug Substances and Drug Products" June 1998) for site-specific stability data, Section VII-I, Table 12, the original NDA long-term and accelerated data from 3 lots produced at B&L Waterford, all production scale and packaged in the container closure system proposed for marketing (with the exception of the above proposed minor packaging modifications). The long term timepoint for the three B&L Waterford site-specific batches will be provided during the CMC RU review period. Does FDA concur with the stability data plan for the NDA?

*FDA Response: Acceptable. Comparison release rate profiles for the drug products made at the two sites should be provided.*

**Proposal 14:**

A CMC Outline highlighting information and data to be included in Module 3 is provided herein (7.0 CMC Plan, "Module 3 Outline," page 50). Does FDA have any questions/comments on the information provided in the outline?

*FDA Response: Acceptable.*

**Proposal 15:**

A Table of Contents for each of the three reviewable units is provided. Does FDA agree with the content and organization of each of the RU's?

*FDA Response: No. Module 1 and Module 2 should be submitted as complete Modules and not as partial Modules spread over several reviewable units.*

*It would be acceptable to include the relevant summary for a particular discipline (i.e. Pharm/Tox, Clinical, CMC) in that discipline's reviewable unit. A duplicate of these summaries would be included in the completed Module 2.*

**Proposal 16:**

How many desk copies of the different RU's does FDA require?

- RU 1: Preclinical - Mod 1, 2, 4 - x desk copies
- RU 2: Clinical - Mod 1, 2, Mod 5 - x desk copies
- RU 3: CMC - Mod 1, 2, Mod 3 - x desk copies

***FDA Response: Desk Copies: Module 1 and Module 2: submit 6 copies of each as desk copies in no specific color jackets.***

***Additional technical review copies:***

*Module 1 and Module 2: submit six jackets, color coded and submitted as reviewer copies (tan, red, green, white, yellow, & orange).*

*Module 3: submit two copies; a red-jacketed copy for CMC and a white-jacketed copy for micro-sterility. The field copy should be sent directly to the district office.*

*Module 4: submit one yellow -jacketed copy for Pharm/Tox.*

*Module 5: submit two copies; one tan-jacketed for clinical reviewer and one green-jacketed for statistical reviewer. Additionally, Module 5 should include the PK section which is usually not more than 1 jacket in length.*

*It is not necessary for the PK reviewer to receive the clinical portion of Module 5. It is necessary for the clinical reviewer to receive the PK section. The PK reviewer copy should be orange-jacketed.*

***Additional comments:***

- Provide correlation table for drug substance lots and drug product lots (include lot size and their manufacturing site) used for clinical trials and stability.*
- Provide table to show all formulations used in development.*
- Provide comparative data for the quality of the implant before and after; ——— (appearance, assay, and impurity)*
- Please update the Labeling according to the current standard. For example, the mutagenesis section of labeling should contain study results. If no data are available, new studies should be conducted (if necessary, a Phase 4 commitment can be considered).*

**Minutes Prepared by:** Michael Puglisi  
Project Manager

**Concurrence by:** William Boyd, M.D.  
Clinical Team Leader

Wiley A. Chambers, M.D.  
Deputy Division Director

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

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Wiley Chambers  
6/4/04 03:07:38 PM

May 28, 2004

**BAUSCH  
& LOMB**

Wiley Chambers, M.D., Deputy Director  
Division of Anti-Inflammatory, Analgesic, and  
Ophthalmologic Drug Products (HFD-550)  
Center for Drug Evaluation and Research  
FOOD AND DRUG ADMINISTRATION  
Attention: Central Document Room  
9201 Corporate Blvd  
Rockville, MD 20850

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MAY 28 2004

CDR / CDER

RE: **NDA 21-737**  
**Fluocinolone Acetonide Intravitreal Implant**  
**Pre-submission of Original Preclinical Reviewable Unit**

RECEIVED

JUN 02 2004

MEGA / CDER

Dear Dr. Chambers:

**NDA NO 21-737** REF NO. 001  
**NDA SUPPL FOR** RUP

Reference is made to IND 60,000 for the Fluocinolone Acetonide Intravitreal Implant (FAII). Reference is also made to Fast Track designation granted by FDA on 04/28/00, Orphan Drug designation granted on 08/03/00, and CMA Pilot 1 Program approval granted on 01/26/04 to Bausch & Lomb for the FAII for the treatment of non-infectious posterior uveitis.

Pursuant to Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, and the CMA Pilot 1 Program under PDUFA III, Bausch & Lomb is hereby submitting the first reviewable unit of a New Drug Application for the above referenced Fast Track product for the localized treatment of non-infectious posterior uveitis.

This first reviewable unit (RU) consists of a complete preclinical section, pertinent administrative documents, and prescribing information in the format of the Common Technical Document (CTD) as follows:

- Module 1: Overall Table of Contents (TOC), FDA Form 356h, User Fee Cover Sheet, Waivers, GLP Certification, FDA/Contacts/Meetings, Draft Package Insert (preclinical section only)
- Module 2: Section 2.1, 2.2, 2.4, 2.6
- Module 4: Nonclinical Study Reports

The submission consists of thirteen (13) volumes. Each module is bound in separate volumes and all documents are separated by tab identifiers. The required archival copy (blue-jacketed) and Pharmacology Toxicology technical review copy (yellow-jacketed) are being sent to the Central Document Room. These are complete sets of the submission. In addition, as requested by FDA at the May 10, 2004 Pre-NDA Meeting, additional technical review copies of Modules 1 and 2 are also being sent to the Central

DUPLICATE

Document Room as follows: tan, red, green, orange, and white-jacketed copies. Six (6) desk copies of Modules 1 and 2 are also being sent to the attention of DAAODP Project Manager Raphael Rodriguez for distribution as needed.

Consistent with the previously agreed upon CMA Pilot I submission schedule for this Fast Track NDA (refer to Module 1, Section 1.15.1, 1/26/04 CMA Pilot 1 approval letter), this reviewable unit will be followed by the second reviewable unit consisting of a complete clinical section in CTD format on August 31, 2004. A complete CMC section in CTD format is scheduled for submission on September 30, 2004 as the last reviewable unit.

As agreed upon with FDA at the May 10, 2004 Pre-NDA Meeting, B&L will be submitting relevant sections of Module 1 and Module 2 with the Preclinical Reviewable Unit and with the Clinical Reviewable Unit. A complete Module 1 and Module 2 will be submitted with the last reviewable unit (i.e, CMC section). This would mean that previously submitted sections from Modules 1 and 2 will be resubmitted with the last reviewable unit.

The information in this submission is confidential and as such should be handled in accordance with the provisions established under 21 CFR 314.430.

If you have any questions regarding this application, please contact me at (813) 866-2568 or by facsimile at (813) 975-7757.

Sincerely,



Yelen Concepcion  
Manager, Regulatory Affairs – Pharmaceuticals  
E-mail: Yelen\_concepcion@bausch.com

Appears This Way  
On Original



IND 60,000

Bausch & Lomb, Inc.  
Attention: Yelen Concepcion  
Associate Manager, Regulatory Affairs  
8500 Hidden River Parkway  
Tampa, FL 33637

Dear Ms. Concepcion:

We acknowledge receipt of your correspondence dated December 8, 2003, requesting confirmation to participate in the Pilot 1 - Continuous Marketing Applications, under the program for rolling submission of sections of an NDA (section 506 of the Federal Food, Drug, and Cosmetic Act) for Fluocinolone Acetonide Intravitreal Implant for the treatment of non-infectious posterior uveitis.

We refer to your Fast Track designation granted by the Division on April 28, 2000, and Orphan designation granted on August 3, 2000, for the Fluocinolone Acetonide Intravitreal Implant for the treatment of non-infectious posterior uveitis.

We also refer to your letter dated December 12, 2003, proposing the following timeline for submission of your complete common technical document (CTD) modules:

| Module Number  | Reviewable Unit | Review Section | Planned Submission Dates |
|--|-----------------|----------------|--------------------------|
| <b>Module 4:</b><br>Preclinical Study Reports<br><b>Module 2:</b><br>Section 2.1, 2.2, 2.4, 2.5<br><b>Module 1:</b> Overall TOC, 356h, User Fee Cover Sheet, Waiver, GLP certification, draft Package Insert | 1               | Preclinical    | May 28, 2004             |
| <b>Module 5:</b> Clinical study Reports<br><b>Module 2:</b> Section 2.1, 2.5, 2.7  | 2               | Clinical       | August 31, 2004          |

|  |                   |                             |                    |
|--|-------------------|-----------------------------|--------------------|
| <b>Module 1:</b> Overall TOC, Debarment, Financial Disclosure, GCP Certification, Draft Package Insert   |                   |                             |                    |
| <b>Module 3:</b> Quality<br><b>Module 2:</b> Section 2.1, 2.3<br><b>Module 1:</b> Overall TOC, Patent Information, Claimed Exclusivity, Field Copy Certification, Environmental Assessment, GMP Certification, Letter of Authorization, Labeling | Completion of NDA | Chemistry and Manufacturing | September 30, 2004 |

In accordance with the Guidance for Industry – Continuous Marketing Applications: Pilot 1 – Reviewable Units for Fast Track Products under PDUFA, the Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products agrees that each of the proposed technical submissions would represent a complete technical section and would be considered a reviewable unit (RU). We have reviewed your request and have concluded that the proposed plan for two RU sections of the NDA is acceptable and your application is accepted into the Pilot 1 program as of the date of this letter.

The Division will issue a discipline review letter within 6 months of the date of receipt of the each RU submission.

The Division recommends a PreNDA meeting prior to submitting the first reviewable unit. Address all additional rolling submissions as follows:

U.S. Postal Service:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Anti-Inflammatory, Analgesic,  
and Ophthalmologic Drug Products, HFD-550  
5600 Fishers Lane  
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Anti-Inflammatory, Analgesic,  
and Ophthalmologic Drug Products, HFD-550  
9201 Corporate Boulevard  
Rockville, Maryland 20850

Send the submission that completes this application and is intended to start the review clock to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Central Document Room  
5901-B Ammendale Rd  
Beltsville, Maryland 20705-1266

If you have any questions, call Raphael R. Rodriguez, Project Manager, at (301) 827-2090.

Sincerely,

*{See appended electronic signature page}*

Wiley A. Chambers, M.D.  
Deputy Director  
Division of Anti-Inflammatory, Analgesic, and  
Ophthalmologic Drug Products, HFD-550  
Office of Drug Evaluation V  
Center for Drug Evaluation and Research

Appears This Way  
On Original

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

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Wiley Chambers  
1/26/04 08:38:34 AM

**Fluocinolone Acetonide Intravitreal Implant for Posterior Uveitis**

**FDA Attendees**

Jonca Bull  
Wiley Chambers  
William Boyd  
Jennifer Harris  
Lucious Lim  
Matt Feinsod  
Stan Lin  
Terri Rumble  
Lori Gorski  
Lisa Hubbard  
Mike Puglisi  
Raphael Rodriguez

**Bausch & Lomb**

Don Handley  
Timothy Comstock  
Tom Crescuillo  
Chao Chen  
Matt Jonasse  
Dean Cirotta

**Consultants**

- I. Assuming the 415-001 study, which is a large (278 subjects), multicenter (27 sites) trial, demonstrates efficacy of the implant in treating uveitis, would the agency accept this single study to support approval for this orphan indication?

**FDA response: No. At least two adequate and controlled studies are required for an NDA submission.**

- II. If the agency agrees with Question #1 and will accept the 415-001 study as providing sufficient evidence of efficacy to support approval of the application, B&L proposes to follow the hierarchy of analyses proposed in Section 4 of the Briefing Document and base a demonstration of efficacy on the body of evidence from all stated comparisons. Does the agency concur with this plan?

**FDA response: See response to #1.**

- III. Since only 4 cases of uveitis-related recurrences have been confirmed in the 415-001 trial it is unlikely that a dose response will be demonstrated for the primary efficacy outcome stated in the protocol (see attached protocol, Section 8.1). B&L will analyze the secondary efficacy measures as well as safety parameters for evidence of a dose response. In the event that a dose response is not shown based on efficacy results, will the agency accept a dose response based on safety measures?

**FDA response: A dose response based on safety results could be used to set an upper limit, but not a lower limit of the dose.**

**The use of multiple secondary endpoints requires adjustments for multiplicity. Additionally, an obvious issue is whether the secondary endpoint(s) is clinically as important as the primary.**

- IV. If the response to Question #1 is that two trials are required, B&L proposes splitting the 415-001 trial into two separate trials based on the rank-ordered block sequence shown in Section 1.3.2 of the Briefing Document.

**Fluocinolone Acetonide Intravitreal Implant for Posterior Uveitis**

- a. Does the agency concur with the rank-ordered block sequence as an acceptable approach to splitting the 415-001 trial into two trials?

**FDA response: The two adequate and controlled studies should demonstrate replication of efficacy results. Splitting, if it were to occur, should have been done prior to any interim or final analyses. If it is performed, it should be based on geographic location difference (i.e., different sides of the ocean, different sides of the Mississippi river, etc.).**

- b. With the splitting of 415-001 into two trials, B&L proposes to analyze the two individual trials using within patient comparisons as shown in Section 4.1 of the Briefing Document to demonstrate efficacy of the product.
- i. Does the agency concur with the within patient comparison of recurrence in the implanted eye at 34 weeks after implantation to recurrence in the 12 months prior to implantation as a basis for efficacy in the individual trials? Do you also concur with the analysis of secondary efficacy variables pre- and post-implantation as further evidence of efficacy?

**FDA response: No. No. If the trial fails its primary efficacy variable, it is a failed trial.**

- ii. Does the agency concur with the within patient comparison of recurrence between the implanted and unimplanted eyes of patients as a basis for efficacy in the individuals trials? Do you also concur with the analysis of secondary efficacy variables between implanted and unimplanted eyes of patients as further evidence of efficacy?

**FDA response: No. No. If the trial fails its primary efficacy variable, it is a failed trial.**

- V. The 2 mg implant was re-designed approximately mid-way through the study due to a stability failure. B&L understands the need to demonstrate similarity between the original and re-designed 2mg implants in order to pool the data. This entails a subgroup analysis of the safety and efficacy measures on the 2 cohorts of patients (one enrolled prior to the stability failure, the other enrolled post stability failure with the re-designed implant).

If the 2 mg subgroup analysis does not demonstrate similarity, the cohort of patients who received the original 2 mg implants will not be used in efficacy analyses. As stated in Section 4 of the Briefing Document, B&L intends to use all patients who received the 0.5 mg implant in all analyses regardless of when they were randomized. Does the agency concur?

**FDA response: Agree.**

- VI. Regardless of the answers to the previous questions, the definition for the primary efficacy outcome of recurrence of uveitis in the current 415-001 protocol (Protocol Section 8.1) does not sufficiently distinguish true recurrences of uveitis versus inflammation due to other clinical reasons (e.g., post-operative inflammation). B&L intends to amend the protocol to add more specificity to the definition of uveitis-related recurrences. Does the agency concur?

**FDA response: The agency needs to review the specifics of the proposal prior to any determination of acceptability.**

- VII. The preclinical program planned for the NDA is outlined in the attached 505(b)(2) proposal. Assuming that the animal and human pharmacokinetic data show negligible systemic exposure, B&L is not planning on conducting any additional animal ADME or safety studies to support the NDA beyond those identified. Does FDA concur with the preclinical safety program intended to support the NDA?

**IND 60,000 End of Phase 2 meeting**

**February 12, 2003**

**Fluocinolone Acetonide Intravitreal Implant for Posterior Uveitis**

**FDA response:** The listed non-clinical studies are adequate to support the submission of NDA. Because of the design change of 2 mg implant during the trial, the results from chronic animal studies should be evaluated in light of the formulation differences. The sponsor needs to clarify which implant formulations were used in the animal studies and human studies.

**Additional comments:** The agency will accept a rolling NDA submission w/ CTD format, and will receive a priority review.

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this page is the manifestation of the electronic signature.**  
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/s/

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Wiley Chambers  
3/3/03 12:42:47 PM



IND 60,000

Yelen Concepcion  
Bausch & Lomb, Inc.  
8500 Hidden River Parkway  
Tampa, FL 33637

Dear Sponsor:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Fluocinolone Acetonide Intravitreal Implant.

We also refer to your amendment dated 7/19/2002, serial number 054, containing information about a new protocol.

The purpose of this letter is to inform you about the Clinical Trials Data Bank available to the public through the Internet at <http://clinicaltrials.gov>. The National Institutes of Health (NIH) through its National Library of Medicine (NLM), and with input from the FDA and others, developed the Clinical Trials Data Bank, as required by the Food and Drug Modernization Act of 1997 (Modernization Act).

Section 113 of the Modernization Act amends 42 U.S.C. 282 and requires the establishment of a public resource for information on studies of drugs for serious or life-threatening diseases conducted under FDA's Investigational New Drug (IND) regulations (21 CFR part 312). It directs the Secretary of Health and Human Services, acting through the Director of NIH, to establish, maintain, and operate a data bank of information on clinical trials for drugs for serious or life-threatening diseases and conditions.

The Clinical Trials Data Bank is intended to be a central resource, providing current information on clinical trials to individuals with serious or life-threatening diseases, other members of the public, healthcare providers, and researchers. Specifically, the Clinical Trials Data Bank will contain 1) information about clinical trials, both federally and privately funded, of experimental treatments for patients with serious or life-threatening diseases; 2) a description of the purpose of each experimental drug; 3) patient eligibility criteria; 4) the location of clinical trial sites, and 5) a point of contact for those wanting to enroll in the trial. This information must be submitted if the clinical trial concerns a serious or life-threatening disease or condition and if the trial tests effectiveness.

FDA has made available a final guidance to implement Section 113 of the Modernization Act. The guidance describes the type of information to submit and how to submit information about clinical trials for serious or life-threatening diseases or conditions to the Clinical Trials Data Bank.

The guidance entitled "Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions" was made available on March 18, 2002. It is accessible through the Internet at <http://www.fda.gov/cder/guidance/4856fnl.htm>

The data fields and their definitions are available in the Protocol Registration System at <http://prsinfo.clinicaltrials.gov/>. Protocols listed in this system will be made available to the public on the Internet at <http://clinicaltrials.gov>.

Please review the referenced protocol to determine if it is a trial for a serious disease or condition and if it is a trial to test effectiveness. If the protocol meets these criteria, you must submit information about the trial to the Clinical Trials Data Bank, unless you provide detailed certification to FDA that such a disclosure would substantially interfere with the timely enrollment of subjects in the investigation (42 U.S.C. 282(j)(3) and (j)(4)). You can also submit information about clinical trials under IND that do not meet the criteria described in the Modernization Act.

We appreciate your cooperation. This project is a collaborative effort by the FDA Office of Special Health Issues, the FDA Center for Drug Evaluation and Research (CDER), and NLM/NIH. You will receive a similar letter for each new protocol submitted to a CDER IND during 2002. If you have any questions, contact Theresa Toigo or Janelle Ernat in the Office of Special Health Issues at (301) 827-4460 or e-mail at [113trials@oc.fda.gov](mailto:113trials@oc.fda.gov).

Sincerely,

*{See appended electronic signature page}*

Janet Woodcock, M.D.  
Director  
Center for Drug Evaluation and Research

*{See appended electronic signature page}*

Theresa Toigo, RPh, MBA  
Director  
Office of Special Health Issues  
Office of Communications and Constituent Relations  
Office of the Commissioner

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this page is the manifestation of the electronic signature.**  
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/s/

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Terry Toigo  
12/24/02 10:14:25 AM

Deborah Henderson  
1/3/03 03:38:28 PM  
for Janet Woodcock, M.D.

6 Page(s) Withheld

b § 552(b)(4) Trade Secret / Confidential

\_\_\_\_\_ § 552(b)(4) Draft Labeling

\_\_\_\_\_ § 552(b)(5) Deliberative Process

## 7/31/00 Orphan Drug Designation



DEPARTMENT OF HEALTH & HUMAN SERVICES

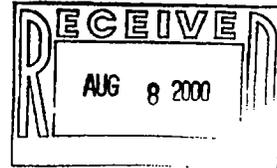
Public Health Service

Office of Orphan Products Development (HF-35)  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857

July 31, 2000

Bausch and Lomb Pharmaceuticals, Inc.  
8500 Hidden River Parkway  
Tampa, Florida 33637

Attention: Samuel A. Bohannon  
Senior Manager, Regulatory Affairs/Project Management



Dear Mr. Bohannon:

Reference is made to the orphan drug application dated February 9, 2000, submitted pursuant to Section 526 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bb) for the designation of fluocinolone acetonide as an orphan drug (application #00-1328). Please also refer to your submission dated May 31, 2000.

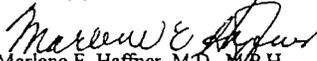
We have completed the review of this application and have determined that fluocinolone acetonide qualifies for orphan designation for the treatment of uveitis involving the posterior segment of the eye.

Please be advised that if your that fluocinolone acetonide is approved for an indication broader than the orphan designation, your product might not be entitled to exclusive marketing rights pursuant to Section 527 of the FDCA (21 U.S.C. 360cc). Therefore, prior to final marketing approval, sponsors of designated orphan drugs are requested to compare the designated orphan indication with the proposed marketing indication and to submit additional data to amend their orphan designation prior to marketing approval if warranted.

Finally, please notify this Office within 30 days of submission of a marketing application for the use of that fluocinolone acetonide as designated. Also an annual progress report must be submitted within 14 months after the designation date and annually thereafter until a marketing application is approved [21 CFR 316.30]. If you need further assistance in the development of your product for marketing, please feel free to contact Robert Pratt, PharmD at (301) 827-3666.

Please refer to this letter as official notification of designation and congratulations on obtaining your orphan drug designation.

Sincerely yours,

  
Marlene E. Haffner, M.D., M.P.H.  
Rear Admiral, United States Public Health Service  
Director, Office of Orphan Products Development

4/28/00 Fast Track Designation



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration  
Rockville MD 20857

IND 60,000

APR 28 2000

Bausch and Lomb Pharmaceuticals, Inc.  
Attn.: Samuel A. Bohannon  
Sr. Manager, Regulatory Affairs/Project Management  
8500 Hidden River Parkway  
Tampa, FL 33637

Dear Mr. Bohannon:

Please refer to your Investigational New Drug Application dated March 2, 2000, received March 6, 2000, submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Fluocinolone Acetonide Intravitreal Implant, and of your request for fast track designation submitted under section 506 of the Act.

We have reviewed your request and have concluded that it meets the criteria for fast track designation as a treatment for a serious disease where there is currently an unmet medical need. Therefore, we are designating Fluocinolone Acetonide Intravitreal Implant for the localized treatment of uveitis involving the posterior segment of the eye as a fast track product.

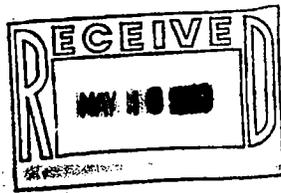
If you pursue a clinical development program that does not support use of Fluocinolone Acetonide Intravitreal Implant for the localized treatment of uveitis involving the posterior segment of the eye, we will not review the application under the fast track development program.

If you have any questions, contact Raphael R. Rodriguez, Project Manager, at (301) 827-2090.

Sincerely,

  
Wiley A. Chambers, M.D.

Deputy Director  
Division of Anti-Inflammatory, Analgesic  
and Ophthalmic Drug Products, HFD-550  
Office of Drug Evaluation V  
Center for Drug Evaluation and Research



### 3/10/00 IND 60,000 Acknowledgement



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville MD 20857

IND 60,000

MAR 10 2000

Bausch and Lomb Pharmaceuticals, Inc.  
ATTN: Samuel A. Bohannon  
Sr. Manager, Regulatory Affairs/Project Management  
8500 Hidden River Parkway  
Tampa, FL 33637

Dear Mr. Bohannon:

We acknowledge receipt of your Investigational New Drug Application (IND) submitted pursuant to section 505(I) of the Federal Food, Drug, and Cosmetic Act, and of your request for fast track designation submitted under section 506 of the Act. Please note the following identifying data:

IND Number Assigned: 60,000

Sponsor: Bausch and Lomb Pharmaceuticals, Inc.

Name of Drug: Fluocinolone Acetonide Intravitreal Implant (0.5 mg, 2 mg, 6 mg)

Proposed Fast Track Indication: Uveitis involving the posterior segment of the eye.

Date of Submission: March 2, 2000

Date of Receipt: March 6, 2000

Studies in humans may not be initiated until 30 days after the date of receipt shown above. If, within the 30-day waiting period, we identify deficiencies in the IND that require correction before human studies begin or that require restriction of human studies until correction, we will notify you immediately that the study may not be initiated ("clinical hold") or that certain restrictions must be placed on it. In the event of such notification, you must continue to withhold, or to restrict, such studies until you have submitted material to correct the deficiencies, and we have notified you that the material you submitted is satisfactory.

It has not been our policy to object to a sponsor, upon receipt of this acknowledgement letter, either obtaining supplies of the investigational drug or shipping it to investigators listed in the IND. However, if the drug is shipped to investigators, they should be reminded that studies may not begin under the IND until 30 days after the IND receipt date or later if the IND is placed on clinical hold.

IND 60,000  
Page 2

As sponsor of this IND, you are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the implementing regulations (Title 21 of the Code of Federal Regulations). Those responsibilities include (1) reporting any unexpected fatal or life-threatening adverse experience associated with use of the drug by telephone or fax no later than 7 calendar days after initial receipt of the information (21 CFR 312.32(c)(2)); (2) reporting any adverse experience with use of the drug that is both serious and unexpected in writing no later than 15 calendar days of initial receipt of the information (21 CFR 312.32(c)(1)); and (3) submitting annual progress reports (21 CFR 312.33).

With regard to your request for fast track designation, we are reviewing your request and we will respond to you within 60 days of the above receipt.

Please forward all future communications concerning this IND in triplicate, identified by the above IND number, and addressed as follows:

U.S. Postal Service

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Anti-Inflammatory, Analgesic,  
and Ophthalmic Drug Products, HFD-550  
Attention: Document Control Room  
5600 Fishers Lane  
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Anti-Inflammatory, Analgesic,  
and Ophthalmic Drug Products, HFD-550  
Attention: Document Control Room  
9201 Corporate Blvd.  
Rockville, Maryland 20850

If you have any questions, contact Raphael R. Rodriguez, Project Manager, at (301) 827-2090.

Sincerely,



Leslie Vaccari  
Chief, Project Management Staff  
Division of Anti-Inflammatory, Analgesic  
and Ophthalmic Drug Products, HFD-550  
Office of Drug Evaluation V  
Center for Drug Evaluation and Research

**See Instructions on Reverse Side Before Completing This Form**

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdufa/default.htm>

1. APPLICANT'S NAME AND ADDRESS

Bausch & Lomb, Inc.  
8500 Hidden River Parkway  
Tampa, FL 33637

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

NDA 21-737

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

YES  NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

The required clinical data will be submitted with the Clinical Reviewable Unit scheduled for August 31, 2004  
(APPLICATION NO. CONTAINING THE DATA).

2. TELEPHONE NUMBER (Include Area Code)

( 813 ) 866-2568

3. PRODUCT NAME

Fluocinolone Acetonide Intravitreal Implant, 0.59 mg / Retisert

6. USER FEE I.D. NUMBER

N/A

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92  
(Self Explanatory)

A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE  
(See item 7, reverse side before checking box.)

THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act  
(See item 7, reverse side before checking box.)

THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY  
(Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

YES  NO

(See Item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes 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  
CBER, HFM-99  
1401 Rockville Pike  
Rockville, MD 20852-1448

Food and Drug Administration  
CDER, HFD-94  
and 12420 Parklawn Drive, Room 3046  
Rockville, MD 20852

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.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE

*Yelen Concepcion*

TITLE

Manager, Regulatory Affairs

DATE

05/28/04

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338  
Expiration Date: August 31, 2005  
See OMB Statement on page 2.

**APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,  
OR AN ANTIBIOTIC DRUG FOR HUMAN USE**  
(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER  
21-737

**APPLICANT INFORMATION**

|  |  |
|--|--|
| NAME OF APPLICANT<br>Bausch & Lomb, Inc.   | DATE OF SUBMISSION<br>10/07/04   |
| TELEPHONE NO. (Include Area Code)<br>(813) 866-2568  | FACSIMILE (FAX) Number (Include Area Code)<br>(813) 975-7757   |
| APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):<br>8500 Hidden River Parkway<br>Tampa, FL 33637 | AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE |

**PRODUCT DESCRIPTION**

|  |  |  |
|--|--|--|
| NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued) 21-737 |  |  |
| ESTABLISHED NAME (e.g., Proper name, USP/USAN name)<br>Fluocinolone Acetonide                                    | PROPRIETARY NAME (trade name) IF ANY<br>Retisert |  |
| CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any)   | CODE NAME (if any)                               |  |
| DOSAGE FORM:<br>Intravitreal Implant   | STRENGTHS:<br>0.59 mg                            | ROUTE OF ADMINISTRATION:<br>Intravitreal |

(PROPOSED) INDICATION(S) FOR USE:  
Non-infectious posterior uveitis

**APPLICATION DESCRIPTION**

|   |
|---|
| APPLICATION TYPE (check one)<br><input checked="" type="checkbox"/> NEW DRUG APPLICATION (CDA, 21 CFR 314.50) <input type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)<br><input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)  |
| IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input type="checkbox"/> 505 (b)(1) <input checked="" type="checkbox"/> 505 (b)(2)   |
| IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION<br>Name of Drug _____ Holder of Approved Application _____  |
| TYPE OF SUBMISSION (check one)<br><input checked="" type="checkbox"/> ORIGINAL APPLICATION <input type="checkbox"/> AMENDMENT TO APENDING APPLICATION <input type="checkbox"/> RESUBMISSION<br><input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT<br><input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input type="checkbox"/> OTHER |

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: January 26, 2004

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY  CBE  CBE-30  Prior Approval (PA)

REASON FOR SUBMISSION  
Original NDA

PROPOSED MARKETING STATUS (check one)  PRESCRIPTION PRODUCT (Rx)  OVER THE COUNTER PRODUCT (OTC)

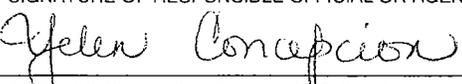
NUMBER OF VOLUMES SUBMITTED 238 THIS APPLICATION IS  PAPER  PAPER AND ELECTRONIC  ELECTRONIC

**ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)**  
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See attachment to this form.

**Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)**

IND 60,000 NDA 20-569 NDA 20-841

|   |   |  |
|---|---|--|
| <b>This application contains the following items: (Check all that apply)</b>  |   |  |
| <input checked="" type="checkbox"/>   | 1. Index  |  |
| <input checked="" type="checkbox"/>   | 2. Labeling (check one)   | <input checked="" type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling   |
| <input checked="" type="checkbox"/>   | 3. Summary (21 CFR 314.50 (c))  |  |
| <input checked="" type="checkbox"/>   | 4. Chemistry section  |  |
| <input checked="" type="checkbox"/>   | A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)                 |  |
| <input type="checkbox"/>  | B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)                            |  |
| <input checked="" type="checkbox"/>   | C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)                                      |  |
| <input type="checkbox"/>  | 5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)                    |  |
| <input checked="" type="checkbox"/>   | 6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)                 |  |
| <input type="checkbox"/>  | 7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))  |  |
| <input checked="" type="checkbox"/>   | 8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)  |  |
| <input type="checkbox"/>  | 9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)  |  |
| <input checked="" type="checkbox"/>   | 10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)   |  |
| <input checked="" type="checkbox"/>   | 11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)   |  |
| <input checked="" type="checkbox"/>   | 12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)  |  |
| <input checked="" type="checkbox"/>   | 13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))                            |  |
| <input checked="" type="checkbox"/>   | 14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A)) |  |
| <input type="checkbox"/>  | 15. Establishment description (21 CFR Part 600, if applicable)  |  |
| <input checked="" type="checkbox"/>   | 16. Debarment certification (FD&C Act 306 (k)(1))   |  |
| <input checked="" type="checkbox"/>   | 17. Field copy certification (21 CFR 314.50 (l)(3))   |  |
| <input checked="" type="checkbox"/>   | 18. User Fee Cover Sheet (Form FDA 3397)  |  |
| <input checked="" type="checkbox"/>   | 19. Financial Information (21 CFR Part 54)  |  |
| <input type="checkbox"/>  | 20. OTHER (Specify)   |  |
| <b>CERTIFICATION</b>  |   |  |
| <p>I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:</p> <ol style="list-style-type: none"> <li>1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.</li> <li>2. Biological establishment standards in 21 CFR Part 600.</li> <li>3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.</li> <li>4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.</li> <li>5. Regulations on making changes in application in FD&amp;C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.</li> <li>6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.</li> <li>7. Local, state and Federal environmental impact laws.</li> </ol> <p>If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.</p> <p>The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.</p> <p><b>Warning:</b> A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.</p> |   |  |
| SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT  | TYPED NAME AND TITLE  | DATE:  |
|   | Yelen Concepcion<br>Manager, Regulatory Affairs   | 10/7/04  |
| ADDRESS (Street, City, State, and ZIP Code)   |   | Telephone Number   |
| 8500 Hidden River Parkway, Tampa, FL 33637  |   | ( 813 ) 866-2568   |
| <p><b>Public reporting burden for this collection of information</b> is estimated to average 24 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:</p>   |   |  |
| Department of Health and Human Services<br>Food and Drug Administration<br>CDER, HFD-99<br>1401 Rockville Pike<br>Rockville, MD 20852-1448  | <b>Food and Drug Administration</b><br>CDER (HFD-94)<br>12229 Wilkins Avenue<br>Rockville, MD 20852             | 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. |

## NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

| Application Information  |  |                                     |
|--|--|-------------------------------------|
| NDA 21-737   | Efficacy Supplement Type SE-   | Supplement Number                   |
| Drug: RETISERT (fluocinolone acetonide intravitreal implant) 0.59mg  |  | Applicant: Bausch & Lomb, Inc.      |
| RPM: Raphael R. Rodriguez  |  | HFD- 550      Phone# (301) 827-2090 |
| <p>Application Type: <input checked="" type="checkbox"/> 505(b)(1)   <input type="checkbox"/> 505(b)(2)<br/>                     (This can be determined by consulting page 1 of the NDA Regulatory Filing Review, if completed for this application. If not completed, or you otherwise have questions about whether an application is a 505(b)(1) or 505(b)(2) NDA, see Appendix A.)</p> <p><b>If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information that is no longer correct.</b></p> <p>( ) Confirmed and/or corrected</p> | <p>Reference Listed Drug (NDA #, Drug name):</p> <p><b>NDA# 12-787</b> Synalar (fluocinolone acetonide) Cream, 0.025%, and Synemol (fluocinolone acetonide) Cream, 0.025%<br/> <b>NDA# 13-960</b> Synalar (fluocinolone acetondie) Ointment, 0.025%<br/> <b>NDA# 15-296</b> Synalar (fluocinolone acetonide) Topical Solution, 0.1%<br/> <b>NDA# 19-452</b> Derma-Smoothe/FS (fluocinolone acetonide) Topical Oil, 0.01%.<br/> <b>NDA# 20-001</b> FS Shampoo, 0.01% (Fluocinolone acetonide) Topical 0.01%.<br/> <b>NDA# 21-112</b> Trilumatm Cream (fluocinolone acetonide 0.01%, hydroquinone 4%, tretinoin 0.05%)</p> |                                     |
| ❖ Application Classifications:   |  |                                     |
| <ul style="list-style-type: none"> <li>• Review priority</li> <li>• Chem class (NDAs only)</li> <li>• Other (e.g., orphan, OTC)</li> </ul>   | ( ) Standard <input checked="" type="checkbox"/> Priority<br><b>3P</b><br><b>Orphan Designation 7/31/2000</b>  |                                     |
| ❖ User Fee Goal Dates  |  |                                     |
| 4/8/2005   |  |                                     |
| ❖ Special programs (indicate all that apply)   |  |                                     |
| ( ) None<br>Subpart H<br>( ) 21 CFR 314.510 (accelerated approval)<br>( ) 21 CFR 314.520 (restricted distribution)<br><input checked="" type="checkbox"/> Fast Track <b>4/28/2000</b><br>( ) Rolling Review<br><input checked="" type="checkbox"/> CMA Pilot 1 <b>1/26/2004</b><br>( ) CMA Pilot 2   |  |                                     |
| ❖ User Fee Information   |  |                                     |
| <ul style="list-style-type: none"> <li>• User Fee</li> <li>• User Fee waiver</li> <li>• User Fee exception</li> </ul>  | ( ) Paid   UF ID number<br><br>( ) Small business<br>( ) Public health<br>( ) Barrier-to-Innovation<br>( ) Other (specify) _<br><br><input checked="" type="checkbox"/> Orphan designation <b>7/31/2000</b><br>( ) No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions)  |                                     |

|  |   |
|--|---|
| ❖ Application Integrity Policy (AIP)   |   |
| • Applicant is on the AIP  | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No   |
| • This application is on the AIP   | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No   |
| • Exception for review (Center Director's memo)  |   |
| • OC clearance for approval  |   |
| ❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.   | <input checked="" type="checkbox"/> Verified  |
| ❖ Patent   |   |
| • Information: Verify that form FDA-3542a was submitted.   | <input checked="" type="checkbox"/> Verified  |
| • Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug in the Orange Book and identify the type of certification submitted for each patent.  | 21 CFR 314.50(i)(1)(i)(A)<br><input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input checked="" type="checkbox"/> IV<br><br>21 CFR 314.50(i)(1)<br><input type="checkbox"/> (ii) <input type="checkbox"/> (iii)  |
| • [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be granted effective approval (but may be tentatively approved if it is otherwise ready for approval) until the date that the patent to which the certification pertains expires.  |   |
| • [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice). <i>(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity))</i>  | <input type="checkbox"/> N/A (no paragraph IV certification)<br><input checked="" type="checkbox"/> Verified  |
| • [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a stay of approval is in effect due to patent infringement litigation.<br><br>Answer the following questions for each paragraph IV certification:<br><br>(1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?<br><br>(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)).<br><br><i>If "Yes," skip to question (4) below. If "No," continue with question (2).</i><br><br>(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)?<br><br><i>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 next box below (Exclusivity).</i><br><br><i>If "No," continue with question (3).</i><br><br>(3) Has the patent owner, its representative, or the exclusive patent licensee | <input type="checkbox"/> N/A (no paragraph IV certification)<br><input checked="" type="checkbox"/> Verified<br><br><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No<br><br><input type="checkbox"/> Yes <input type="checkbox"/> No<br><br><input type="checkbox"/> Yes <input type="checkbox"/> No |

filed a lawsuit for patent infringement against the applicant?

(Note: This can be determined by confirming whether the Division has received a written notice from the 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)). The patent owner (or its representative) may, but is not required, to provide such notification (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 next box below (Exclusivity).*

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

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

Yes  No

(Note: This can be determined by confirming whether the Division has received a written notice from the 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)). (The patent owner (or its representative) may, but is not required, to provide such notification (see 21 CFR 314.107(f)(2)). Note that the applicant has until the **later** of the following dates to provide the Division with this written notice: (a) the date marking the end of the 45-day period described in question (1), above, or (b) the date that the Division completes its review of the application (see 21 CFR 314.107(f)(2)).

*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 next box below (Exclusivity).*

*If "Yes," a stay of approval may be in effect; answer the following questions.*

- (6) (a) Was the patent subject to the paragraph IV certification submitted to FDA on or after August 18, 2003?

Yes  No

(Note: This can be determined by checking with [the Orange Book staff?].)

*If "No," skip to question 7. If "Yes," continue with part (b).*

- (b) Was the patent also submitted to FDA before the date that this 505(b)(2) application was submitted as substantially complete?

Yes  No

*If "No," there is no stay of approval based on the paragraph IV certification for this patent. If "Yes," continue with question (7).*

- (7) (a) Have 30 months (or an alternate length of time ordered by the court, if any) passed from the date the patent owner received the applicant's notice of certification for the patent?

Yes  N/A

(Note: In general, approval of a 505(b)(2) application cannot be made effective (although the application can be tentatively approved) for 30 months from the date that the patent owner receives the applicant's notice of certification if a patent infringement suit is timely initiated as described in question (5) above. However, the court may order that the 30-month period be shortened or lengthened under certain circumstances. If the court has ordered that the 30-month period be altered in a particular case, the applicant is required to submit a copy of the court order to the Division within 10 working days (see 21 CFR 314.107(e)).

*If "No," go to question (8). If "Yes," continue with part (b) of this question.*

- (b) Before the expiration of the 30-month (or other) period described in part (a), above, did the district court hearing the patent infringement action decide whether the patent subject to the certification is invalid, unenforceable, or not infringed? (For purposes of this question, a district court decision would include a statement regarding the patent's invalidity, unenforceability, or noninfringement that is part of a settlement order or consent decree entered by the court, or a substantive determination by the court that there is no cause of action for patent invalidity or noninfringement.)

Yes  N/A

(Note: To answer this question, you should check whether the Division has received a copy of a court order or judgment. The applicant is required to submit a copy of any such document to the Division within 10 working days (see 21 CFR 314.107(e)).

*If "No," there is no stay of approval based on the paragraph IV certification for this patent. Analyze the remaining paragraph IV certifications, if any, in this application. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).*

*If "Yes," continue with part (c) of this question.*

- (c) Did the district court decide that the patent was invalid, unenforceable, or not infringed?

Yes  N/A

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

*If "No," (i.e., the district court decided that the patent was valid, enforceable, and infringed), continue with part (d) of this question.*

- (d) If the district court's decision was appealed, has the appellate court issued a decision finding the patent invalid, unenforceable, or not

infringed (including a statement to this effect that is part of a settlement order or consent decree entered by the appellate court, or a substantive determination by the court that there is no cause of action for patent invalidity or noninfringement)?

Yes  N/A

(Note: As mentioned above, the applicant is required to submit a copy of all court orders or judgments to the Division within 10 working days (see 21 CFR 314.107(e)); therefore, you can check to see whether a copy of an appellate court's order or judgment has been submitted.)

*If "Yes," there is no stay of approval based on the paragraph IV certification for this patent. Analyze the remaining paragraph IV certifications, if any, in this application. If there are no other paragraph IV certifications, go to the next box below (Exclusivity).*

*If "N/A" (i.e., the district court decision was not appealed) or "No" (i.e., the appellate court has not yet issued a decision, or has decided that the patent was infringed), the application cannot be effectively approved until the date the patent expires. (If, before the date the patent expires, the appellate court decides that the patent is invalid, unenforceable, or not infringed, the application may be effectively approved as of the date of the appellate decision, if it otherwise qualifies for effective approval.) Analyze the remaining paragraph IV certifications, if any, in this application. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).*

(8) (a) Has the district court hearing the patent infringement action decided whether the patent subject to the certification is invalid, unenforceable, or not infringed? (For purposes of this question, a district court decision would include a statement regarding the patent's invalidity, unenforceability, or noninfringement that is part of a settlement order or consent decree entered by the court, or a substantive determination by the court that there is no cause of action for patent invalidity or noninfringement.)

Yes  N/A

(Note: To answer this question, you should check whether the Division has received a copy of a court order or judgment. The applicant is required to submit a copy of any such document to the Division within 10 working days (see 21 CFR 314.107(e)).

*If "No," a stay of approval is currently in effect until the expiration of the time period described in (7)(a), above. The stay may be terminated or altered if the district court issues a decision regarding the patent's validity, enforceability, or infringement before the expiration of the time period described in (7)(a). If such a decision is issued before this time period expires, answer question (b) below.*

*If "Yes," continue with part (b) of this question.*

(b) Did the district court decide that the patent was invalid, unenforceable, or not infringed?

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

Yes  N/A

*If "No," (i.e., the district court decided that the patent was valid, enforceable, and infringed), continue with part (c) of this question.*

|   |   |
|---|---|
| <p>(c) If the district court's decision was appealed, has the appellate court issued a decision finding the patent invalid, unenforceable, or not infringed (including a statement to this effect that is part of a settlement order or consent decree entered by the appellate court, or a substantive determination by the court that there is no cause of action for patent invalidity or noninfringement)?</p> <p>(Note: As mentioned above, the applicant is required to submit a copy of all court orders or judgments to the Division within 10 working days (see 21 CFR 314.107(e)); therefore, you can check to see whether a copy of an appellate court's order or judgment has been submitted.)</p> <p><i>If "Yes," there is no stay of approval based on the paragraph IV certification for this patent.</i></p> <p><i>If "N/A" (i.e., the district court decision was not appealed) or "No" (i.e., the appellate court has not yet issued a decision, or has decided that the patent was infringed), the application cannot be effectively approved until the date the patent expires. (If, before the date the patent expires, the appellate court decides that the patent is invalid, unenforceable, or not infringed, the application may be effectively approved as of the date of the appellate decision, if it otherwise qualifies for effective approval.) Analyze the remaining paragraph IV certifications, if any, in this application. If there are no other paragraph IV certifications, go to the next box below (Exclusivity).</i></p> | <p>( ) Yes (X) N/A</p>  |
| <p>❖ Exclusivity (approvals only)</p>   |   |
| <ul style="list-style-type: none"> <li>Exclusivity summary</li> <li>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>   | <p>N/A</p>  |
| <ul style="list-style-type: none"> <li>Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!</li> </ul>   | <p>( ) Yes, Application # _____<br/>(X) No</p>  |
| <p>❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)</p>  |   |
| <p style="text-align: center;"><b>General Information</b></p>   |   |
| <p>❖ Actions</p>  |   |
| <ul style="list-style-type: none"> <li>Proposed action <span style="float: right;">4/8/2005</span></li> </ul>   | <p>(X) AP ( ) TA ( ) AE ( ) NA</p>  |
| <ul style="list-style-type: none"> <li>Previous actions (specify type and date for each action taken)</li> </ul>  |   |
| <ul style="list-style-type: none"> <li>Status of advertising (approvals only)</li> </ul>  | <p>( ) Materials requested in TA letter<br/>( ) Reviewed for Subpart H</p>                            |
| <p>❖ Public communications</p>  |   |
| <ul style="list-style-type: none"> <li>Press Office notified of action (approval only)</li> </ul>   | <p>(X) Yes ( ) Not applicable</p>   |
| <ul style="list-style-type: none"> <li>Indicate what types (if any) of information dissemination are anticipated</li> </ul>   | <p>(X) None<br/>( ) Press Release<br/>( ) Talk Paper<br/>( ) Dear Health Care Professional Letter</p> |
| <p>❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))</p>  |   |
| <ul style="list-style-type: none"> <li>Division's proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>  | <p>4/7/2005</p>   |

|   |   |
|---|---|
| • Most recent applicant-proposed labeling   | 4/7/2005                                |
| • Original applicant-proposed labeling  | 10/7/2004                               |
| • Labeling reviews (including DDMAC, DMETS, DSRCs) and minutes of labeling meetings ( <i>indicate dates of reviews and meetings</i> ) | 4/6/2005; 10/5/2001                     |
| • Other relevant labeling (e.g., most recent 3 in class, class labeling)  |   |
| ❖ Labels (immediate container & carton labels)  |   |
| • Division proposed (only if generated after latest applicant submission)   | 3/28/2005                               |
| • Applicant proposed  | 3/31/2005                               |
| • Reviews   | 4/7/2005                                |
| ❖ Post-marketing commitments  |   |
| • Agency request for post-marketing commitments   | 3/31/2005                               |
| • Documentation of discussions and/or agreements relating to post-marketing commitments   | 4/5/2005                                |
| ❖ Outgoing correspondence (i.e., letters, E-mails, faxes)   |   |
| ❖ Memoranda and Telecons  |   |
| ❖ Minutes of Meetings   |   |
| • EOP2 meeting (indicate date)  | 2/12/2003                               |
| • Pre-NDA meeting (indicate date)   | 5/10/2004                               |
| • Pre-Approval Safety Conference (indicate date; approvals only)  | N/A                                     |
| • Other   |   |
| ❖ Advisory Committee Meeting  |   |
| • Date of Meeting   | N/A                                     |
| • 48-hour alert   | N/A                                     |
| ❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)   | N/A                                     |
| <b>Summary Application Review</b>   |   |
| ❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) ( <i>indicate date for each review</i> )            | 4/8/2005                                |
| <b>Clinical Information</b>   |   |
| ❖ Clinical review(s) ( <i>indicate date for each review</i> )   | 4/4/2005; 4/8/2005                      |
| ❖ Microbiology (efficacy) review(s) ( <i>indicate date for each review</i> )  | N/A                                     |
| ❖ Safety Update review(s) ( <i>indicate date or location if incorporated in another review</i> )                                      | 12/14/2004                              |
| ❖ Risk Management Plan review(s) ( <i>indicate date/location if incorporated in another rev</i> )                                     | N/A                                     |
| ❖ Pediatric Page (separate page for each indication addressing status of all age groups)  | EXEMPTED – ORPHAN designation 7/31/2000 |
| ❖ Demographic Worksheet ( <i>NME approvals only</i> )   | N/A                                     |
| ❖ Statistical review(s) ( <i>indicate date for each review</i> )  | 3/7/2005                                |
| ❖ Biopharmaceutical review(s) ( <i>indicate date for each review</i> )  | 2/28/2005                               |
| ❖ Controlled Substance Staff review(s) and recommendation for scheduling ( <i>indicate date for each review</i> )                     | N/A                                     |
| ❖ Clinical Inspection Review Summary (DSI)  |   |
| • Clinical studies  | N/A                                     |
| • Bioequivalence studies  | N/A                                     |

**CONSULTATION RESPONSE**  
**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT**  
**OFFICE OF DRUG SAFETY**  
**(DMETS; HFD-420)**

|   |  |                                 |
|---|--|---------------------------------|
| <b>DATE RECEIVED:</b><br>March 14, 2005 | <b>DESIRED COMPLETION DATE:</b> March 30, 2005<br><b>PDUFA DATE:</b> April 8, 2005 | <b>ODS CONSULT #:</b> 00-0315-1 |
|---|--|---------------------------------|

**TO:** Brian Harvey, M.D.  
 Director, Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products  
 HFD-550

**THROUGH:** Raphael Rodriguez  
 Project Manager  
 HFD-550

|                      |                            |
|----------------------|----------------------------|
| <b>PRODUCT NAME:</b> | <b>NDA SPONSOR:</b> Pfizer |
|----------------------|----------------------------|

**Retisert**  
 (Fluocinolone Acetonide Intravitreal Implant)  
 0.59 mg

**NDA # 21-737**

**SAFETY EVALUATOR:** Linda M. Wisniewski, RN

**RECOMMENDATIONS:**

1. DMETS has no objections to the use of the proprietary name, Retisert. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name and its associated labels and labeling must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.
2. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review in order to minimize user error. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.
3. DDMAC finds the proprietary name Retisert acceptable from a promotional perspective.

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**Division of Medication Errors and Technical Support (DMETS)**  
**Office of Drug Safety**  
**HFD-420; PKLN Rm. 6-34**  
**Center for Drug Evaluation and Research**

**PROPRIETARY NAME REVIEW**

**DATE OF REVIEW:** March 18, 2005

**NDA#** 21-737

**NAME OF DRUG:** **Retisert** (Fluocinolone Acetonide Intravitreal Implant)  
0.59 mg

**IND HOLDER:** Bausch and Lomb, Inc.

**I. INTRODUCTION:**

This consult was written in response to a request from the Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products (HFD-550), for re-assessment of the proprietary name, "Retisert", regarding potential name confusion with other proprietary or established drug names. Retisert was originally found acceptable on October 5, 2001. Draft container, carton and insert labeling were provided for review.

**PRODUCT INFORMATION**

Retisert is a sterile implant for continuous delivery of fluocinolone acetonide locally to the posterior segment of the eye. The Retisert intravitreal implant is designed to release fluocinolone acetonide at a nominal initial rate of 0.6 mcg/day, decreasing over the first month to a steady state of between 0.3 mcg/day to 0.4 mcg/day over approximately 30 months. The active ingredient in the Retisert intravitreal implant is the synthetic corticosteroid fluocinolone acetonide. Each Retisert implant consists of a tablet containing 0.59 mg of the active ingredient. It is indicated for the treatment of chronic non-infectious uveitis affecting the posterior segment of the eye.

The retisert intravitreal implant is surgically implanted into the posterior segment of the affected eye. Following depletion of fluocinolone acetonide from the implant, as evidenced by recurrence of uveitis, Retisert may be replaced or an additional Retisert may be implanted.

Caution should be exercised in handling of the Retisert intravitreal implant in order to avoid damage to the implant, which may result in an increased rate of drug release from the implant. Thus, the Retisert implant should be handled only by the suture tab. Care should be taken to avoid sheer forces on the implant that could disengage the cup reservoir from the suture tab. Aseptic technique should be maintained at all times prior to and during the surgical implantation procedure.

It is supplied as a single, sterile implant containing 0.59 mg of fluocinolone acetonide in a polycarbonate case within a foil pouch designed to maintain product sterility and further packaged within a Tyvek peelable overwrap. Each packaged implant is provided in a carton which includes the package insert.

**II. RISK ASSESSMENT:**

The medication error staff of DMETS conducted a search of several standard published drug product reference texts<sup>1,2</sup> as well as several FDA databases<sup>3</sup> for existing drug names which sound-alike or look-alike to Retisert to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted<sup>4</sup>. The Saegis<sup>5</sup> Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Retisert. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proprietary name Retisert acceptable from a promotional perspective.
2. The Expert Panel identified two proprietary names that were thought to have the potential for confusion with Retisert. These products are listed in Table 1 (see below), along with the dosage forms available and usual dosage. Additionally, the term Retinol was identified as a potential look-alike to Retisert.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

| Product Name  | Dosage form(s), Established name                                     | Usual adult dose*   | Other* |
|---|--|---|--------|
| Retisert  | Fluocinolone Acetonide Intravitreal Implant<br>0.59 mg               | One implant every 30 months as needed   | N/A    |
| Retinol   | Naturally occurring form of Vitamin A                                | N/A   | L/A    |
| Rilutek   | Riluzole Tablets 50 mg   | 50 mg every 12 hours.   | L/A    |
| Rifater   | Rifampin, Isoniazid, and Pyrazinamide Tablets<br>120 mg/50 mg/300 mg | Patient Weight $\leq$ 44 kg = 4 tablets once daily<br>Patient Weight 44-54 kg = 5 tablets once daily<br>Patients Weight $\geq$ 55 kg = 6 tablets once daily | L/A    |
| *Frequently used, not all-inclusive.<br>**L/A (look-alike), S/A (sound-alike) |  |   |        |

<sup>1</sup> MICROMEDEX Integrated Index, 2005, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

<sup>2</sup> Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

<sup>3</sup> AMF Decision Support System [DSS], [Drugs@FDA](mailto:Drugs@FDA), the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, and the electronic online version of the FDA Orange Book.

<sup>4</sup> WWW location <http://www.uspto.gov/tmdb/index.html>.

<sup>5</sup> Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at [www.thomson-thomson.com](http://www.thomson-thomson.com)

B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. All names considered to have significant phonetic or orthographic similarities to Retisert were discussed by the Expert Panel.

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Retisert, the primary concerns related to look-alike confusion with Retinol, Rilutek, and Rifater.

Upon further review of the names gathered from EPD, the name Retinol will not be reviewed further. Retinol is “a 20-carbon primary alcohol occurring as several isomers; it is the form of vitamin A (vitamin A<sub>1</sub>) found in mammals. Most dietary sources occur as esters of retinol, also the predominant forms for storage and transport; the de-esterified alcohol can be converted to the metabolically active forms retinal and retinoic acid” ([www.dorlands.com](http://www.dorlands.com)). Since Retinol is not a marketable product, but a naturally occurring form of Vitamin A, it will not be discussed.

1. Rilutek may look similar to Retisert when written. Rilutek is indicated in the treatment Amyotrophic Lateral Sclerosis (ALS). The first three letters of each name may look similar when scripted (ril vs. ret). However, the rest of the name is orthographically different (isert vs. utek). Although both names have upstrokes in the same positions (third letter and last letter), Rilutek has an additional upstroke in the middle of the name. However, this may not be a differentiating factor because many ‘t’s are not crossed prominently. Therefore, the presentation of the central upstroke may not be obvious and result in similar orthographic presentations of each name. There are some differentiating product characteristics, such as dose (50 mg vs. 0.59 mg), dosage form (tablet vs. intravitreal implant), strength (50 mg vs. 0.59 mg), frequency of administration (every twelve hours vs. every 30 months), route of administration (oral vs. intravitreal), and indication of use (Amyotrophic Lateral Sclerosis vs. uveitis). The most likely location for confusion between Rilutek and Retisert is in a hospital or In/Out Surgical Facility. Retisert will only be distributed to hospitals where it will be implanted into the patient’s eye during a same-day surgical procedure. Although both of these products may be stocked near each other in an inpatient pharmacy, the conditions of use may help to differentiate them. An inpatient order for Rilutek will usually have a route of administration and dosage interval, and it is less likely to be sent to an operating suite since it is an oral drug. In contrast, Retisert will likely be ordered as a floor stock or a ‘charge and replace’ item for the operating room. Additionally, if Retisert is ordered on an inpatient the route of administration would help to differentiate the two names. The product characteristics and location of use will help to differentiate these two products.



2. Rifater may look similar to Retisert when written. Rifater is indicated in the initial phase of the short-course of treatment of pulmonary tuberculosis. Both names begin with the same two letters (ri). However, the remaining letters are orthographically different (fater vs. tisert). The upstroke in each name appears at the third letter (f vs. t), but, the 'f' in Rifater also requires a below-the-line downstroke and the 't' in Retisert requires a cross-bar. Additionally, the last letter of Retisert requires both an upstroke and a cross-bar. Although not all 't's are prominently crossed, the upstroke at the end of the name with or without a cross-bar may help. Moreover, Retisert has one more letter than Rifater (7 letters vs. 8 letters) which contributes to the longer orthographic presentation of Retisert. There are differentiating product characteristics such as dose (0.59 mg vs. 4, 5, or 6 tablets), dosage form (intravitreal implant vs. tablet), strength (0.59 mg vs. 120 mg/50 mg/300 mg), frequency of administration (every 30 months vs. once daily), and route of administration (intravitreal vs. oral). The most likely location for confusion between Rifater and Retisert is in a hospital or In/Out Surgical Facility. Retisert will only be distributed to hospitals where it will be implanted into the patient's eye during a same-day surgical procedure. Although both of these products may be stocked near each other in an inpatient pharmacy, the conditions of use may help to differentiate them. An inpatient order for Rifater will usually have a route of administration, dosage interval, and number of tablets to be given. Rifater is less likely to be sent to an operating suite since it is an oral drug. In contrast, Retisert will likely be ordered as a floor stock or a 'charge and replace' item for the operating room. Additionally, if Retisert is ordered on an inpatient, the route of administration would help to differentiate the two names. The orthographic differences, product characteristics, and the context and location of use will help to differentiate these two products and minimize confusion involving this name pair.

*Retisert*  
*Rifater*

### III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

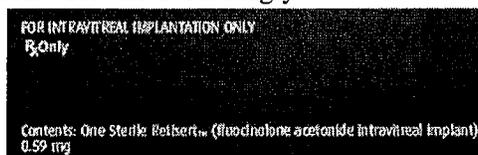
In the review of the container labels, carton and insert labeling of Retisert, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

#### A. CONTAINER LABEL

The most prominent information on the primary display panel should be the proprietary and established names. Presently the NDC Barcode and the manufacturer's name have as much prominence as the proprietary name. Increase the size, font, presentation of the proprietary and established name so that they are the most prominent information on the primary display panel.

#### B. CARTON LABELING

1. The solid blue 'prism-like' graphic is the most prominent item on the primary display panel and is distracting. Additionally, the white print on the contrasting blue background is difficult to read. See below. DMETS recommends revising the color of the text and/or contrasting background to improve legibility and decrease the prominence of the background color. Revise accordingly.



2. DMETS recommends including the directions and graphics for safe handling on the outer carton, so that when the carton is opened and the implant is removed, it will be handled in a manner, which will minimize damage.

C. PACKAGE INSERT LABELING

1. DOSAGE AND ADMINISTRATION section, Handling, and Disposal subsection:

This section refers to the safe handling of the product in order to prevent damage to the implant. We recommend that graphics that describe and demonstrate the safe handling of the product be included in this section in order to prevent inadvertent damage to the implant.

2. HOW SUPPLIED section:

The insert will be packaged in a carton with the implant. We also recommend including the directions and graphics for safe handling on the outer carton, so that when the carton is opened and the implant is removed, it will be handled in a manner, which will minimize damage.

IV. RECOMMENDATIONS:

- A. DMETS has no objections to the use of the proprietary name, Retisert. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name and its associated labels and labeling must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.
- B. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.
- C. DDMAC finds the proprietary name Retisert acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-2102.

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Linda M. Wisniewski, RN  
Safety Evaluator  
Division of Medication Errors and Technical Support  
Office of Drug Safety

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

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Linda Wisniewski  
4/5/05 12:34:50 PM  
DRUG SAFETY OFFICE REVIEWER

Denise Toyer  
4/6/05 10:57:36 AM  
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