

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-598

MICROBIOLOGY REVIEW(S)

Product Quality Microbiology Review
Review for HFD-550

12 MARCH 2003

NDA:
NDA 21-598

Drug Product Name

Proprietary: Moxifloxacin HCl Ophthalmic Solution, 0.5%

Non-proprietary: Moxifloxacin HCl

Drug Product Classification: P

Review Number: 1

Subject of this Review

Submission Date: 14 October 2002

Receipt Date: 15 October 2002

Consult Date: 24 October 2002

Date Assigned for Review: 31 October 2002

Submission History (for amendments only)

Date(s) of Previous Submission(s): N/A

Date(s) of Previous Micro Review(s): N/A

Applicant/Sponsor

Name: Alcon, Inc.

Address: P.O. Box 62; Bosch 69; CH-6331 Hünenberg, Switzerland

Representative: Angela Kothe, Ph.D. Asst. Director, Reg. Affairs

Telephone: 817-551-4933

Name of Reviewer: Bryan S. Riley, Ph.D.

Conclusion: Recommend for Approval

Product Quality Microbiology Data Sheet

- A.
1. TYPE OF SUPPLEMENT: N/A
 2. SUPPLEMENT PROVIDES FOR: N/A
 3. MANUFACTURING SITE: ASPEX
6201 South Freeway
Fort Worth, TX

Kayersberg Manufacturing Facility
Laboratoires Alcon S.A.
Kayersberg, France
 4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: Sterile Ophthalmic Solution in LDPE Bottle w/ Dispensing Plug; 0.5%
 5. METHOD(S) OF STERILIZATION: _____
 6. PHARMACOLOGICAL CATEGORY: Antibiotic
- B. SUPPORTING/RELATED DOCUMENTS: N/A
- C. REMARKS: The drug product will be manufactured in _____
The trade size will be an _____ plastic DROP-TAINER
system : _____

filename: 21458.doc

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ON ORIGINAL**

Executive Summary

I. Recommendations

- A. **Recommendation on Approvability** – This submission is recommended for approval on the basis of product quality microbiology.
- B. **Recommendations on Phase 4 Commitments and/or Agreements, if Approvable** – N/A

II. Summary of Microbiology Assessments

- A. **Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology** – The drug product is _____
- B. **Brief Description of Microbiology Deficiencies** – N/A
- C. **Assessment of Risk Due to Microbiology Deficiencies** – The drug product is _____ using properly validated processes. Therefore, the drug product presents a minimal risk from the standpoint of product quality microbiology.

III. Administrative

- A. **Reviewer's Signature** _____
- B. **Endorsement Block**
Bryan S. Riley, Ph.D. (Microbiology Reviewer)
Peter H. Cooney, Ph.D. (Microbiology Supervisor)
- C. **CC Block**
N/A

14 Page(s) Withheld

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

 § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling

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

/s/

Bryan Riley
3/21/03 01:30:26 PM
MICROBIOLOGIST

Peter Cooney
3/21/03 01:57:51 PM
MICROBIOLOGIST

**APPEARS THIS WAY
ON ORIGINAL**

MICROBIOLOGY REVIEW
DIVISION OF SPECIAL PATHOGEN AND IMMUNOLOGIC DRUG PRODUCTS
(HFD-590)

Consultative Review for HFD-550
Division of Analgesic, Anti-Inflammatory, and Ophthalmic Drug Products

Requestor: Michael Puglisi, CSO HFD-550

Date of Request: October 22, 2002

Reason for Request: Original NDA—request comments on clinical microbiology issues

NDA #: ~~_____~~
21-598

REVIEWER:	Peter A. Dionne
CORRESPONDENCE DATE:	14-OCT-02
CDER DATE:	14-OCT-02
REVIEW ASSIGN DATE:	22-OCT-02
REVIEW COMPLETE DATE:	18-FEB-03

SPONSOR: Alcon Research Ltd.
6201 S. Freeway
Fort Worth, Texas 76134-2099

CONTACT PERSON: Angela C. Kothe, Ph.D.
Assistant Director, Regulatory Affairs
Phone Number: (817) 551-4933

SUBMISSION REVIEWED: Original NDA

DRUG CATEGORY: Antimicrobial: Fluoroquinolone

INDICATIONS: Bacterial Conjunctivitis

DOSAGE FORM: Sterile ophthalmic solution

DRUG PRODUCT NAME

PROPRIETARY:

NONPROPRIETARY/USAN: moxifloxacin hydrochloride ophthalmic solution

CHEMICAL NAME: 1-cyclopropyl-7-[(S,S)-2,8-diazabicyclo(4.3.0)non-8-yl]-6-fluoro-8-methoxy-1,4-dihydro-4-oxo-3-quinolone carboxylic acid hydrochloride

3. Bacteria in general are susceptible to various antimicrobials and resistant to others; often this is an inherent characteristic, or it may be an acquired characteristic. The in vitro finding that bacteria are resistant is not considered for labeling unless such a finding is considered clinically significant, meaning that there is documented evidence that this resistance mechanism is responsible for clinically significant outcomes (e.g., MRSA, VRE). You may consider attending the March 5, 2003 Anti Infective Advisory Committee meeting, where this topic will be discussed at length. Of note, the long list of resistance mechanisms listed for many of the bacteria in the proposed labeling would **NOT** be allowed to be included in the systemic moxifloxacin products without a comprehensive review, including most likely an advisory committee discussion. Of note, some of the company's proposals (e.g. *Staphylococcus aureus*) are erroneous, as addressed below. [You may wish to contact John Powers, Lead Medical Officer for Antimicrobial Drug Product Development and Resistance.]
4. The list of organisms that ODEIV includes in the second, so called in vitro list, are limited to pathogens that are known to be etiologic agents in the indication being approved. The proposed list in the _____ package insert appears quite lengthy.

CONCLUSIONS & RECOMMENDATIONS:

The application is approvable from the microbiological viewpoint under section 505(b) of the Act when the recommended changes are made to the MICROBIOLOGY subsection of the package insert. The changes needed should be sent to the sponsor. These revisions are listed under the section of this review labeled as marked up label (deletions and additions) on pages 15-18.

**APPEARS THIS WAY
ON ORIGINAL**

Microbiological Label Review

The following is a quick review of the Moxifloxacin ophthalmic label. Each organism listed by the sponsor appears in the list below with comments about its susceptibility to moxifloxacin. This review does not take into account whether or not the organism is associated with bacterial conjunctivitis. No review was done of the data submitted in the ophthalmic NDA, all comments are based solely on data from systemic moxifloxacin NDAs that were previously submitted to the Agency.

REASONS FOR DELETIONS AND ADDITIONS TO LABEL

LIST #1 (Clinically Indicated Organisms)

Gram-positive bacteria:

Corynebacterium species—only a few isolates were tested in the original NDA. It appears that the MIC₉₀ is below the susceptible breakpoint. We usually try to have all organisms speciated, but I believe we have allowed this genus into labels before without speciation. OKAY IN LABEL—INDIVIDUAL SPECIES SHOULD BE LISTED IF THEY WERE SPECIATED IN CLINICAL TRIALS.

_____ species—No information about this genus available in moxifloxacin systemic NDAs. THIS GENUS SHOULD BE DELETED UNLESS THERE IS EVIDENCE FROM CLINICAL TRIALS SUBMITTED IN THE OPHTHALMIC NDA.

Micrococcus luteus _____

NO INFORMATION ABOUT THIS SPECIES IS GIVEN IN MOXIFLOXACIN SYSTEMIC NDAs. THIS ORGANISM SHOULD BE DELETED UNLESS THERE IS EVIDENCE FROM CLINICAL TRIALS SUBMITTED IN THE OPHTHALMIC NDA. The _____ should be deleted.

Staphylococcus aureus _____

_____ SHOULD BE ALLOWED AS STAPHYLOCOCCUS AUREUS. _____ THIS ORGANISM IS IN THE MOXIFLOXACIN SYSTEMIC LABEL.

Staphylococcus epidermidis (

ALLOWED AS *STAPHYLOCOCCUS EPIDERMIDIS* / SHOULD BE
THIS ORGANISM IS IN THE MOXIFLOXACIN SYSTEMIC LABEL

Staphylococcus haemolyticus

This organism was only tested in a limited number of studies in the moxifloxacin systemic NDAs. Not enough evidence was provided to allow it into the systemic label. THIS ORGANISM SHOULD BE DELETED UNLESS THERE IS EVIDENCE FROM CLINICAL TRAILS SUBMITTED IN THE OPHTHALMIC NDA.

Staphylococcus hominis

This organism was only tested in a limited number of studies in the moxifloxacin systemic NDAs. Not enough evidence was provided to allow it into the systemic label. THIS ORGANISM SHOULD BE DELETED UNLESS THERE IS EVIDENCE FROM CLINICAL TRAILS SUBMITTED IN THE OPHTHALMIC NDA.

Staphylococcus warneri

-This organism was only tested in a limited number of studies in the systemic NDAs. Not enough testing was performed to allow it into the moxifloxacin systemic label. has not been allowed in labels. THIS ORGANISM SHOULD BE DELETED UNLESS THERE IS EVIDENCE FROM CLINICAL TRAILS SUBMITTED IN THE OPHTHALMIC NDA.

This organism is
FROM THE LABEL.

THIS SPECIES SHOULD BE DELETED

Streptococcus pneumoniae

STREPTOCOCCUS PNEUMONIAE
ORGANISM IS IN THE MOXIFLOXACIN SYSTEMIC LABEL.

THIS SPECIES SHOULD BE LISTED AS
THIS

Streptococcus viridans

— THIS GROUP OF ORGANISMS SHOULD BE LISTED
AS **STREPTOCOCCUS VIRIDANS GROUP**.
— THIS GROUP OF ORGANISMS IS IN THE MOXIFLOXACIN SYSTEMIC
LABEL.

Gram-negative bacteria:

Acinetobacter

— There were a limited
amount of data available in the moxifloxacin systemic NDAs on *A. baumannii*, *A. calcoaceticus*, and *A. lwoffii*. One study that tested only 15 isolates had a high MIC₉₀ value. All other studies had MIC₉₀s well below the susceptible breakpoint.
— MAY REMAIN IN THE LABEL.

— -No information is available on this species from the
moxifloxacin systemic NDAs. THIS SPECIES SHOULD BE DELETED FROM THE
LABEL.

Haemophilus influenzae

— THIS SPECIES SHOULD BE LISTED AS **HAEMOPHILUS
INFLUENZAE**. THIS SPECIES IS IN THE MOXIFLOXACIN SYSTEMIC LABEL.

— -ALLOWED IN LABEL. THIS SPECIES IS IN THE
MOXIFLOXACIN SYSTEMIC LABEL.

— -ALLOWED IN LABEL. THIS SPECIES IS IN THE
MOXIFLOXACIN SYSTEMIC LABEL.

Other microorganisms:

Chlamydia trachomatis—A limited amount of data are available on this organism in the moxifloxacin systemic NDAs. The species appears to be susceptible to moxifloxacin. THIS ORGANISM IS ALLOWED TO BE IN THE LABEL. IT IS NOT IN THE MOXIFLOXACIN SYSTEMIC LABEL SINCE SYSTEMIC MOXIFLOXACIN IS NOT APPROVED FOR OCULAR OR GENITAL INFECTIONS.

LIST #2 (*In vitro* Activity)

The introduction to this listing is not correct. This introduction should be identical to that in other fluoroquinolone ophthalmic labels. To be placed in this *in vitro* activity listing the following criteria must be met:

1. Susceptibility testing on 50 to 100 isolates of the organism must have been performed in multiple studies.
2. The MIC₉₀ values in the susceptibility testing studies must be less than or equal to the susceptible breakpoint for the systemic drug.
3. The organism must be relevant to the proposed indication(s).

Gram-positive bacteria:

— -No information on this species was available in the moxifloxacin systemic NDAs. THIS SPECIES SHOULD BE DELETED FROM THE LABEL.

— -No information on this genus was available in the moxifloxacin systemic NDAs. THIS GENUS SHOULD BE DELETED FROM THE LABEL.

— -No information on this species was available in the moxifloxacin systemic NDAs. THIS SPECIES SHOULD BE DELETED FROM THE LABEL. |

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— -No information on this species was available in the moxifloxacin systemic NDAs. THIS SPECIES SHOULD BE DELETED FROM THE LABEL.

— -No information on this genus was available in the moxifloxacin systemic NDAs. THIS GENUS SHOULD BE DELETED FROM THE LABEL.

— that are listed SHOULD NOT BE ALLOWED SINCE IS ALREADY LISTED IN FIRST LIST.

— -Several studies in the moxifloxacin systemic NDAs had high MICs. THIS SPECIES SHOULD BE DELETED FROM THE LABEL.

— -Most studies in the moxifloxacin systemic NDAs had high MICs. THIS SPECIES SHOULD BE DELETED FROM THE LABEL.

— Only a limited amount of data on this species was provided in the moxifloxacin systemic NDAs. NOT ENOUGH TESTING WAS PERFORMED TO ALLOW THIS SPECIES IN THE LABEL.

— No information on this species was available in the moxifloxacin systemic NDAs. THIS SPECIES SHOULD BE DELETED FROM THE LABEL.

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— No information on this species was available in the moxifloxacin systemic NDAs. THIS SPECIES SHOULD BE DELETED FROM THE LABEL. INDIVIDUAL SPECIES SHOULD NOT BE LISTED IF THE GENUS IS ALLOWED IN LIST #1.

— No information on this species was available in the moxifloxacin systemic NDAs. THIS SPECIES SHOULD BE DELETED FROM THE LABEL. INDIVIDUAL SPECIES SHOULD NOT BE LISTED IF THE GENUS IS ALLOWED IN LIST #1.

— No information on this species was available in the moxifloxacin systemic NDAs. THIS SPECIES SHOULD BE DELETED FROM THE LABEL. INDIVIDUAL SPECIES SHOULD NOT BE LISTED IF THE GENUS IS ALLOWED IN LIST #1.

— No information on this genus was available in the moxifloxacin systemic NDAs. THIS GENUS SHOULD BE DELETED FROM THE LABEL. THE GENUS SHOULD NOT BE LISTED IF *MICROCOCCLUS LUTEUS* IS ALLOWED IN LIST #1.

— No information on this genus was available in the moxifloxacin systemic NDAs. THIS GENUS SHOULD BE DELETED FROM THE LABEL.

— No information on this genus was available in the moxifloxacin systemic NDAs. THIS GENUS SHOULD BE DELETED FROM THE LABEL.

— No information on this species was available in the moxifloxacin systemic NDAs. THIS SPECIES SHOULD BE DELETED FROM THE LABEL.

— -No information on this species was available in the moxifloxacin systemic NDAs. THIS SPECIES SHOULD BE DELETED FROM THE LABEL.

— -Only a limited amount of data on this species was available in the moxifloxacin systemic NDAs. THIS SPECIES SHOULD BE DELETED FROM THE LABEL.

— -No information on this species was available in the moxifloxacin systemic NDAs. THIS SPECIES SHOULD BE DELETED FROM THE LABEL.

— -Only a limited amount of data on this species was available in the moxifloxacin systemic NDAs. THIS SPECIES SHOULD BE DELETED FROM THE LABEL.

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— -Only a limited amount of data on this species was available in the moxifloxacin systemic NDAs. THIS SPECIES SHOULD BE DELETED FROM THE LABEL.

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— -Only a limited amount of data on this species was available in the moxifloxacin systemic NDAs. THIS SPECIES SHOULD BE DELETED FROM THE LABEL.

— -No information on this species was available in the moxifloxacin systemic NDAs. THIS SPECIES SHOULD BE DELETED FROM THE LABEL.

— -This species is _____ and is, therefore, already listed in the label. THIS SPECIES SHOULD BE DELETED SINCE IT IS A MEMBER OF THE VIRIDANS GROUP.

— -No information on this species was available in the moxifloxacin systemic NDAs. THIS SPECIES SHOULD BE DELETED FROM THE LABEL.

— -No information on this species was available in the moxifloxacin systemic NDAs. THIS SPECIES SHOULD BE DELETED FROM THE LABEL.

— -No information on this species was available in the moxifloxacin systemic NDAs. THIS SPECIES SHOULD BE DELETED FROM THE LABEL.

— This species is a member of viridans group, and is, therefore, already listed in the label. THIS SPECIES SHOULD BE DELETED SINCE IT IS A MEMBER OF THE VIRIDANS GROUP.

— This species is a member of viridans group, and is, therefore, already listed in the label. THIS SPECIES SHOULD BE DELETED SINCE IT IS A MEMBER OF THE VIRIDANS GROUP.

Streptococcus pyogenes—This species is in the moxifloxacin systemic label. THIS SPECIES MAY REMAIN IN THE LABEL.

— -This species is a member of viridans group, and is, therefore, already listed in the label. THIS SPECIES SHOULD BE DELETED SINCE IT IS A MEMBER OF THE VIRIDANS GROUP.

— -This species is a member of viridans group, and is, therefore, already listed in the label. THIS SPECIES SHOULD BE DELETED SINCE IT IS A MEMBER OF THE VIRIDANS GROUP.

— -No information on this species was available in the moxifloxacin systemic NDAs. THIS SPECIES SHOULD BE DELETED FROM THE LABEL.

— This species is a member of viridans group, and is, therefore, already listed in the label. THIS SPECIES SHOULD BE DELETED SINCE IT IS A MEMBER OF THE VIRIDANS GROUP.

Gram-negative bacteria:

— No information on this species was available in the moxifloxacin systemic NDAs. THIS SPECIES SHOULD BE DELETED FROM THE LABEL.

All — species that are listed SHOULD NOT BE ALLOWED SINCE
— SPECIES IS ALREADY IN LIST #1.

— No information on this species was available in the moxifloxacin systemic NDAs. THIS SPECIES SHOULD BE DELETED FROM THE LABEL.

— No information on this species was available in the moxifloxacin systemic NDAs. THIS SPECIES SHOULD BE DELETED FROM THE LABEL. IF — SPECIES (see next item) IS LISTED THEN INDIVIDUAL SPECIES SHOULD NOT BE LISTED.

— No information on this genus was available in the moxifloxacin systemic NDAs. THIS GENUS SHOULD BE DELETED FROM THE LABEL.

— No information on this species was available in the moxifloxacin systemic NDAs. THIS SPECIES SHOULD BE DELETED FROM THE LABEL.

— No information on this species was available in the moxifloxacin systemic NDAs. THIS SPECIES SHOULD BE DELETED FROM THE LABEL.

— Only a limited amount of data on this species was available in the moxifloxacin systemic NDAs. THIS SPECIES SHOULD BE DELETED FROM THE LABEL.

— No information on this genus was available in the moxifloxacin systemic NDAs. THIS GENUS SHOULD BE DELETED FROM THE LABEL.

— Many studies in the moxifloxacin systemic NDAs had high MICs. THIS SPECIES SHOULD BE DELETED FROM THE LABEL.

— This species is in the moxifloxacin systemic label. THIS SPECIES MAY REMAIN IN THE LABEL.

— No information on this species was available in the moxifloxacin systemic NDAs. THIS SPECIES SHOULD BE DELETED FROM THE LABEL.

Escherichia coli—This species is in the moxifloxacin systemic label. THIS SPECIES MAY REMAIN IN THE LABEL.

— No information on this species was available in the moxifloxacin systemic NDAs. THIS SPECIES SHOULD BE DELETED FROM THE LABEL.

— species—No information on this species was available in the moxifloxacin systemic NDAs. THIS SPECIES SHOULD BE DELETED FROM THE LABEL.

Klebsiella oxytoca—This species is in the moxifloxacin systemic label. THIS SPECIES MAY REMAIN IN THE LABEL.

— No information on this species was available in the moxifloxacin systemic NDAs. THIS SPECIES SHOULD BE DELETED FROM THE LABEL.

—No information on this species was available in the moxifloxacin systemic NDAs. THIS SPECIES SHOULD BE DELETED FROM THE LABEL.

—Many studies in the moxifloxacin systemic NDAs had high MICs. THIS SPECIES SHOULD BE DELETED FROM THE LABEL.

—SHOULD PROBABLY BE LISTED AS INDIVIDUAL SPECIES. LIMITED DATA AVAILABLE ON ANY SPECIES OTHER THAN

—No information on this species was available in the moxifloxacin systemic NDAs. THIS SPECIES SHOULD BE DELETED FROM THE LABEL.

—No information on this species was available in the moxifloxacin systemic NDAs. THIS SPECIES SHOULD BE DELETED FROM THE LABEL.

—No information on this species was available in the moxifloxacin systemic NDAs. THIS SPECIES SHOULD BE DELETED FROM THE LABEL.

Proteus mirabilis—This species is in the moxifloxacin systemic label. THIS SPECIES MAY REMAIN IN THE LABEL.

—Only a limited amount of data on this species was available in the moxifloxacin systemic NDAs. Many studies in the moxifloxacin systemic NDAs had high MICs. THIS SPECIES SHOULD BE DELETED FROM THE LABEL.

—No information on this species was available in the moxifloxacin systemic NDAs. THIS SPECIES SHOULD BE DELETED FROM THE LABEL.

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—No information on this genus was available in the moxifloxacin systemic NDAs. THIS GENUS SHOULD BE DELETED FROM THE LABEL.

— -No information on this species was available in the moxifloxacin systemic NDAs. THIS SPECIES SHOULD BE DELETED FROM THE LABEL.

— -No information on this genus was available in the moxifloxacin systemic NDAs. THIS GENUS SHOULD BE DELETED FROM THE LABEL.

— -No information on this species was available in the moxifloxacin systemic NDAs. THIS SPECIES SHOULD BE DELETED FROM THE LABEL.

— -Many studies in the moxifloxacin systemic NDAs had high MIC₉₀s. THIS SPECIES SHOULD BE DELETED FROM THE LABEL.

— -No information on this genus was available in the moxifloxacin systemic NDAs. THIS GENUS SHOULD BE DELETED FROM THE LABEL.

— -Many studies in the moxifloxacin systemic NDAs had high MIC₉₀ values. THIS SPECIES SHOULD BE DELETED FROM THE LABEL.

Anaerobic microorganisms:

Fusobacterium species—This genus is in the moxifloxacin systemic label. THIS GENUS MAY REMAIN IN THE LABEL.

— No information on this genus was available in the moxifloxacin systemic NDAs. THIS GENUS SHOULD BE DELETED FROM THE LABEL.

— No information on this species was available in the moxifloxacin systemic NDAs. THIS SPECIES SHOULD BE DELETED FROM THE LABEL.

— -Only a limited amount of data on this genus was available in the moxifloxacin systemic NDAs. THIS GENUS SHOULD BE DELETED FROM THE LABEL.

Prevotella species—This genus is in the moxifloxacin systemic label. THIS GENUS MAY REMAIN IN THE LABEL.

— -Only a limited amount of data on this species was available in the moxifloxacin systemic NDAs. THIS SPECIES SHOULD BE DELETED FROM THE LABEL.

— -Only a limited amount of data on this genus was available in the moxifloxacin systemic NDAs. THIS GENUS SHOULD BE DELETED FROM THE LABEL.

Other Organisms:

— This genus is only allowed in labels if an indication for them is given. THIS GROUP SHOULD BE DELETED FROM THE LABEL.

— This species is in the systemic label. This species is usually associated with respiratory tract infections.

— This species is in the systemic label. This species is usually associated with respiratory tract infections.

— This species is in the systemic label. This species is usually associated with respiratory tract infections.

MARKED UP LABEL (DELETIONS AND ADDITIONS)

In order to be as consistent as possible with the moxifloxacin systemic label the opening paragraphs of the microbiology subsection should be altered to read the same as the tablet label. What the sponsor proposed is almost identical but minor changes have been made. Deletions to the sponsor's label are indicated by a strikeout. Additions to the sponsor's label are indicated by a double underline.

The microbiology subsection should read as follows:

5 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

**APPEARS THIS WAY
ON ORIGINAL**

Peter A. Dionne
Microbiologist HFD-590

CONCURRENCES:

HFD-590/Div Dir _____ Signature _____ Date _____
HFD-590/TLMicro _____ Signature _____ Date _____

CC:

HFD-550/Original NDA
HFD-590/Division File
HFD-590/Micro/PDionne
HFD-590/SCSO/Efrank
HFD-590/MO/LLim
HFD-590/Pharm/ZChen
HFD-590/BioPharm/HLu
HFD-590/Chem/STso
HFD-590/CSO/MPuglisi

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

/s/

Peter Dionne
2/21/03 03:08:52 PM
MICROBIOLOGIST

Shukal signed on 2/22/03

Shukal Bala
2/28/03 09:51:59 AM
MICROBIOLOGIST

Renata Albrecht
2/28/03 03:55:38 PM
MEDICAL OFFICER

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