CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-212

MICROBIOLOGY REVIEW(S)

Product Quality Microbiology Review

23-JUNE-2008

NDA: 22-212/N-000/BZ
22-212/N-000/BC

Drug Product Name
Proprietary: DUREZOL (proposed)
Non-proprietary: Difluprednate
Drug Product Priority Classification: Priority

Review Number: 2

Dates of Submission(s) Covered by this Review

Letter	Stamp	Review Request	Assigned to Reviewer
6/11/08	6/11/08	N/A	N/A
6/18/08	6/18/08	N/A	N/A

Submission History (for amendments only):

Submission Date(s)	Microbiology Review #	Review Date(s)
12/21/07	1	5/9/08
4/25/08	1	5/9/08

Applicant/Sponsor
Name: Sirion Therapeutics, Inc.,
Address: 3110 Cherry Palm Drive
Suite 340
Tampa, FL 33619

Representative: Christine Miller, PharmD
Telephone: (813) 496-7325 ext. —

Name of Reviewer: Stephen E. Langille, Ph.D.

Conclusion: Recommended for approval

Product Quality Microbiology Data Sheet

A. 1. **TYPE OF SUBMISSION:** Amendment to the original submission

2. **SUBMISSION PROVIDES FOR:** [redacted], operation for a sterile topical ophthalmic product.

3. **MANUFACTURING SITE:** [redacted]

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**

- Ophthalmic emulsion
- Topical
- 0.05%
- 5 mL multi-dose ophthalmic bottles [redacted]
- [redacted] 5 mL fill volumes

5. **METHOD(S) OF STERILIZATION:** [redacted]

6. **PHARMACOLOGICAL CATEGORY:** anti-inflammatory

B. **SUPPORTING/RELATED DOCUMENTS:** A number of e-mailed responses to microbiology information requests were submitted by the applicant and routed through the project manager in order to expedite the product quality microbiology review. The applicant provided a commitment to submit this information in a formal amendment to the NDA.

C. **REMARKS:** The application was submitted in eCTD format. An initial quality assessment was entered into DFS on 2/19/08. Product quality microbiology information requests were sent to the applicant on 3/24/08 and 4/14/08. Responses to these requests were provided on 4/25/08. A brief teleconference was held with Sirion manufacturing and regulatory affairs personnel on 5/5/08 to discuss unresolved product quality microbiology issues and additional information requests were made by e-mail on 5/6/08. The applicant provided a response via e-mail on 5/7/08. The applicant provided additional product quality microbiology information via e-mail throughout late May and early July of 2008. The applicant has provided a commitment to submit all of this information in an official amendment to the application.

filename: N022212R2.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability -

NDA 22-212 is recommended for approval from the standpoint of product quality microbiology.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable -

Not applicable

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology -

B. Brief Description of Microbiology Deficiencies -

No product quality microbiology deficiencies were identified based upon the information provided.

C. Assessment of Risk Due to Microbiology Deficiencies -

Not applicable

III. Administrative

A. Reviewer's Signature _____
Stephen E. Langille, Ph.D.

B. Endorsement Block
David Hussong, Ph.D.

C. CC Block
N/A

5 Page(s) Withheld

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

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Microbiology- 1

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/s/

Stephen Langille
6/23/2008 02:07:44 PM
MICROBIOLOGIST

David Hussong
6/23/2008 02:38:47 PM
MICROBIOLOGIST
I concur with the microbiology reviewer's recommendation that this application may be recommended for approval.

Product Quality Microbiology Review

9-May-2008

NDA: 22-212

Drug Product Name
Proprietary: DUREZOL (proposed)
Non-proprietary: Difluprednate
Drug Product Priority Classification: Priority

Review Number: 1

Dates of Submission(s) Covered by this Review

Letter	Stamp	Review Request	Assigned to Reviewer
12/21/08	12/26/08	12/28/07	1/3/08
4/25/08	4/25/08	N/A	N/A

Submission History (for amendments only): Not applicable

Applicant/Sponsor
Name: Sirion Therapeutics, Inc.,
Address: 3110 Cherry Palm Drive
Suite 340
Tampa, FL 33619

Representative: Christine Miller, PharmD
Telephone: (813) 496-7325 ext.

Name of Reviewer: Stephen E. Langille, Ph.D.

Conclusion: Approvable

Product Quality Microbiology Data Sheet

A. 1. **TYPE OF SUBMISSION:** Original Submission

2. **SUBMISSION PROVIDES FOR:** [redacted] operation for a sterile topical ophthalmic product.

3. **MANUFACTURING SITE:** 5 3

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**

- Ophthalmic emulsion
- Topical
- 0.05%
- 5 mL multi-dose ophthalmic bottles [redacted]
- [redacted] 5 mL fill volumes

5. **METHOD(S) OF STERILIZATION:** [redacted]

6. **PHARMACOLOGICAL CATEGORY:** anti-inflammatory

B. **SUPPORTING/RELATED DOCUMENTS:** None

C. **REMARKS:** The application was submitted in eCTD format. An initial quality assessment was entered into DFS on 2/19/08. Product quality microbiology information requests were sent to the applicant on 3/24/08 and 4/14/08. Responses to these requests were provided on 4/25/08. A brief teleconference was held with Sirion manufacturing and regulatory affairs personnel on 5/5/08 to discuss unresolved product quality microbiology issues and additional information requests were made by e-mail on 5/6/08. The applicant provided a response via e-mail on 5/7/08.

filename: N022212R1.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability -

NDA 22-212 is approvable pending the resolution of product quality microbiology deficiencies.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable -

Not applicable

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology -

B. Brief Description of Microbiology Deficiencies -

The applicant failed to provide the following information:

C. Assessment of Risk Due to Microbiology Deficiencies -

Failure to address the product quality microbiology deficiencies could lead to microbial and/or endotoxin contamination of the drug product.

III. Administrative

A. Reviewer's Signature _____
Stephen E. Langille, Ph.D.

B. Endorsement Block
James McVey – Team Leader

C. CC Block
N/A

14 Page(s) Withheld

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

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Microbiology- 2

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/s/

Stephen Langille
5/12/2008 02:28:03 PM
MICROBIOLOGIST

James McVey
5/12/2008 02:43:07 PM
MICROBIOLOGIST
I concur.

MEMORANDUM

Date: June 9, 2008

To: NDA 22-212

From: David Hussong, Ph.D.
Associate Director for New Drug Microbiology
OPS/CDER

Subject: Tertiary review of OPS-Microbiology recommendation for NDA 22-212 Durezol (difluprednate ophthalmic emulsion) 0.05%.

The OPS-Microbiology Review of NDA 22-212 was completed by Dr. Stephen Langille (DFS date 12-MAY-2008) with the identification of five issues to be resolved before recommending approval of the application. These issues relate to:

1. [redacted]
2. validation of the sterilizing filter's retentive capacity,
3. validation of the sterilization of process for [redacted] equipment,
4. failure to provide acceptance criteria and a suitable test for endotoxins in the finished product (for batch release), and
5. product preparation methods, quality criteria (related to sterility) and the supplier (manufacturer) of the tips and caps for the container system.

The applicant responded on 28-MAY-2008, with information addressing issues 1, 3, 4, and 5. Item 2 was the subject of an email date 2-June-2008. However, amendments to the NDA have not been reviewed yet, and only item 4 (endotoxins-related issues) can be considered resolved based on the email. The other items require review.

Since the unresolved items have potentially significant risk to patient safety, I concur with the Microbiology Reviewer's recommendation that the NDA should be APPROVABLE for microbiology aspects of CMC.

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/s/

David Hussong
6/9/2008 04:48:16 PM
MICROBIOLOGIST

This memorandum provides the division director's tertiary review concurring with the primary reviewer's recommendation of APPROVABLE for the NDA.

Deliverables by Mid-Cycle for Product Quality Microbiology

(1) Team participation requested, submission received and assigned to Microbiology reviewer (by day 21).

(2) Microbiology reviewer performs filing review and a preliminary review of draft labeling (by day 45).

(3) Microbiology reviewer completes the filing checklist and identifies filing issues and/or other major deficiencies. Checklist is signed off in DFS by secondary reviewer/Team Leader (by day 45).

(4) When potential fileability issues or serious deficiencies are identified, the Microbiology reviewer attends the filing meeting and presents the filing issues and/or deficiencies to be communicated to the applicant.

(5) First review completed prior to mid-cycle meeting with secondary reviewer's concurrence. Information request sent soon after completion of the first review (by month 5).

(6) Microbiology reviewer attends appropriate team meetings and the mid-cycle meeting and presents findings accordingly.

(7) Reviewer and secondary reviewer/Team Leader communicate frequently regarding the review status, submission data and deficiencies.

PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

NDA Number: 22-212 **Applicant:** SIRiON Therapeutics **Letter Date:** 12/21/07

Drug Name: DUREZOL (proposed) **NDA Type:** Priority **Stamp Date:** December 26, 2007

The following are necessary to initiate a review of the NDA application:

	Content Parameter	Yes	No	Comments
1	Is the product quality microbiology information described in the NDA and organized in a manner to allow substantive review to begin? Is it legible, indexed, and/or paginated adequately?	X		
2	Has the applicant submitted an overall description of the manufacturing processes and microbiological controls used in the manufacture of the drug product?	X		
3	Has the applicant submitted protocols and results of validation studies concerning microbiological control processes used in the manufacture of the drug product?	X		
4	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?		X	
5	Has the applicant submitted preservative effectiveness studies (if applicable) and container-closure integrity studies?	X		
6	Has the applicant submitted microbiological specifications for the drug product and a description of the test methods?	X		
7	Has the applicant submitted the results of analytical method verification studies?	X		
8	Has the applicant submitted all special/critical studies/data requested during pre-submission meetings and/or discussions?	X		
9	Is this NDA fileable? If not, then describe why.	X		

Additional Comments: Additional container closure integrity test data, media fill data and equipment sterilization validation data may be required, but the application is fileable.

Reviewing Microbiologist
Stephen E. Langille

Date

Microbiology Secondary Reviewer/Team Leader
James McVey

Date

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/s/

Stephen Langille
1/28/2008 07:26:51 AM
MICROBIOLOGIST
Filing checklist for NDA 22-212 - DUREZOL topical ophthalmic

James McVey
1/29/2008 08:25:20 AM
MICROBIOLOGIST