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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-516

Microbiology Review(s)

Product Quality Microbiology Review
Review for HFD-550
27-April-2004

NDA: 21-516-BZ

Drug Product Name

Proprietary: ISTALOL®

Non-proprietary: 0.5% timolol maleate ophthalmic solution

Drug Product Classification: Standard

Review Number: 3

Subject of this Review

Submission Date: December 6, 2003

Receipt Date: December 8, 2003

Consult Date: December 16, 2003

Date Assigned for Review: December 18, 2003

Submission History (for amendments only)

Date(s) of Previous Submission(s): September 25, 2002 and
June 5, 2003

Date(s) of Previous Micro Review(s): March 3, 2003 and
October 11, 2003

Applicant/Sponsor

Name: Senju Pharmaceutical Co., Ltd.

Address: 5-8 Hiranomachi 2-chome
Chou-ku
Osaka 541-0046
Japan

Representative: Marvin Garrett
ISTA Pharmaceuticals, Inc.

Telephone: 949-788-5303

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

Conclusion:

Recommended for Approval

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Product Quality Microbiology Data Sheet

- A.
1. TYPE OF SUPPLEMENT: Not applicable
 2. SUPPLEMENT PROVIDES FOR: Not applicable
 3. MANUFACTURING SITE: Bausch & Lomb
Pharmaceuticals, Inc.
8500 Hidden River Parkway
Tampa, FL 33637
 4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:
 - Sterile ophthalmic solution
 - Topical Ocular
 - 0.5%
 5. METHOD(S) OF STERILIZATION:
 6. PHARMACOLOGICAL CATEGORY: Ophthalmic solution
- B. SUPPORTING/RELATED DOCUMENTS: None
- C. REMARKS: Amendments were submitted to the agency on June 5, 2003, June 16, 2003 and June 23, 2003 in response to the original Microbiology Review completed on March 3, 2003. Amendment 21-516-BZ was submitted on December 6, 2003.

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Executive Summary

I. Recommendations

- A. Recommendation on Approvability -**
NDA 21-516 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 -**
The drug product is: []
Container/closure components are: []
[] at a contract facility. The manufacturing equipment is: []
- B. Brief Description of Microbiology Deficiencies -**
No deficiencies were identified based upon the information provided.
- C. Assessment of Risk Due to Microbiology Deficiencies -**
Not applicable

III. Administrative

- A. Reviewer's Signature** _____
- B. Endorsement Block**
Stephen E. Langille, Ph.D.
Peter Cooney, Ph.D.
- C. CC Block**
In DFS

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/s/

Stephen Langille
5/12/04 08:33:32 AM
MICROBIOLOGIST

Peter Cooney
5/12/04 08:46:26 AM
MICROBIOLOGIST

Product Quality Microbiology Review
Review for HFD-550
26-SEP-2003

NDA: 21-516-BI

Drug Product Name

Proprietary: ISTALOL®
Non-proprietary: 0.5% timolol maleate ophthalmic
solution
Drug Product Classification: Standard

Review Number: 2

Subject of this Review

Submission Date: June 5, 2003
Receipt Date: June 6, 2003
Consult Date: June 10, 2003
Date Assigned for Review: June 28, 2003

Submission History (for amendments only)

Date(s) of Previous Submission(s): September 25, 2002
Date(s) of Previous Micro Review(s): March 3, 2003

Applicant/Sponsor

Name: Senju Pharmaceutical Co., Ltd.
Address: 5-8 Hiranomachi 2-chome
Chou-ku
Osaka 541-0046
Japan

Representative: Marvin Garrett
ISTA Pharmaceuticals, Inc.

Telephone: 949-788-5303

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

Conclusion: Approvable pending revision

Product Quality Microbiology Data Sheet

- A.
1. **TYPE OF SUPPLEMENT:** Not applicable
 2. **SUPPLEMENT PROVIDES FOR:** Not applicable
 3. **MANUFACTURING SITE:** J
 4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**
 - Sterile ophthalmic solution
 - Topical Ocular
 - 0.5%
 5. **METHOD(S) OF STERILIZATION:** J
 6. **PHARMACOLOGICAL CATEGORY:** Ophthalmic solution
- B. **SUPPORTING/RELATED DOCUMENTS:** DMF J
- C. **REMARKS:** Amendments were submitted to the agency on June 5, 2003, June 16, 2003 and June 23, 2003 in response to the original Microbiology Review completed on March 3, 2003.

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Executive Summary

I. Recommendations

- A. Recommendation on Approvability -**
NDA 21-516 is approvable pending the revision of 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 -**
The drug product is []
Container/closure components are []
[] at a contract facility. The manufacturing equipment is []
- B. Brief Description of Microbiology Deficiencies -**
The applicant should provide the results of container closure integrity testing and antimicrobial preservative effectiveness testing using the new product containers.
- C. Assessment of Risk Due to Microbiology Deficiencies -**
Failure to address container closure integrity and preservative effectiveness issues could lead to contamination of the product following its release from the manufacturing site.

III. Administrative

- A. Reviewer's Signature** _____
- B. Endorsement Block**
Stephen E. Langille, Ph.D.
Peter Cooney, Ph.D.
- C. CC Block**
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/s/

Stephen Langille
10/17/03 10:57:47 AM
MICROBIOLOGIST

Peter Cooney
10/17/03 11:02:56 AM
MICROBIOLOGIST

Product Quality Microbiology Review

Review for HFD-550

20 Feb. 2003

NDA: 21-516

Drug Product Name

Proprietary: BRANDNAME 0.5%
Non-proprietary: timolol ophthalmic solution
Drug Product Classification: Standard

Review Number: 1

Subject of this Review

Submission Date: September 25, 2002
Receipt Date: September 26, 2002
Consult Date: October 1, 2002
Date Assigned for Review: October 21, 2002

Submission History (for amendments only)

Date(s) of Previous Submission(s):
Date(s) of Previous Micro Review(s):

Applicant/Sponsor

Name: Senju Pharmaceutical Co., Ltd.
Address: 5-8 Hiranomachi 2-chome
Chou-ku
Osaka 541-0046
Japan

Representative:

Telephone:

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

Conclusion: Approvable pending revision

Product Quality Microbiology Data Sheet

- A.
1. TYPE OF SUPPLEMENT: Not applicable
 2. SUPPLEMENT PROVIDES FOR: Not applicable
 3. MANUFACTURING SITE:
- 1
4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:
 - Sterile ophthalmic solution
 - Topical Ocular
 - 0.5%
 5. METHOD(S) OF STERILIZATION:
 6. PHARMACOLOGICAL CATEGORY: Ophthalmic solution
- B. SUPPORTING/RELATED DOCUMENTS: DMF
- C. REMARKS: Product quality microbiology information was provided in volume 5 of this NDA. Some validation information is provided in DMF The applicant did not provide a letter of authorization for this DMF or specify the location of the pertinent information within this DMF.

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Executive Summary

I. Recommendations

- A. Recommendation on Approvability -**
NDA 21-516 is approvable pending the revision of microbiology deficiencies.
- B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable -**

II. Summary of Microbiology Assessments

- A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology -**
The drug product is []
Container/closure components are []
The manufacturing equipment is []
- B. Brief Description of Microbiology Deficiencies -**
The applicant should provide the following:
- []
 - []
 - []
 - []
 - []
 - Additional information regarding container/closure integrity testing
 - Sterility testing as part of the stability protocol
- C. Assessment of Risk Due to Microbiology Deficiencies -**
The number and variety microbiological deficiencies identified represents a significant risk to microbiology product quality. Additional information is required to determine the risk of microbial contamination in the final drug product.

III. Administrative

- A. **Reviewer's Signature** _____
- B. **Endorsement Block**
Stephen E. Langille, Ph.D.
Peter Cooney, Ph.D.
- C. **CC Block**
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/s/

Stephen Langille
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MICROBIOLOGIST

Peter Cooney
3/4/03 10:21:43 AM
MICROBIOLOGIST