

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22382Orig1s000

MICROBIOLOGY REVIEW(S)

Product Quality Microbiology Review

02 OCTOBER 2009

NDA: 22-382/N-000

Drug Product Name

Proprietary: SPRIX

Non-proprietary: Ketorolac Tromethamine Nasal Spray

Review Number: 2

Dates of Submission(s) Covered by this Review

<u>Submit Date</u>	<u>Received</u>	<u>Review Request</u>	<u>Assigned to Reviewer</u>
25 September 2009	28 September 2009	28 September 2009	28 September 2009

Submission History (for amendments only)

<u>Submission Date(s)</u>	<u>Microbiology Review #</u>	<u>Review Date(s)</u>
05 December 2008	1	22 September 2009

Applicant/Sponsor

Name: ROXRO PHARMA, Inc.

Address: 535 Middlefield Road, Suite 180
Menlo Park, CA 94025

Representative: Bonnie Horner
Regulatory Consultant

Telephone: 650-279-2315
650-947-9776
bonniehorner@sbcglobal.net

Name of Reviewer: Robert J. Mello, Ph.D.

Conclusion: The application is recommended for approval from microbiology product quality standpoint.

Product Quality Microbiology Data Sheet

- A. 1. **TYPE OF SUBMISSION:** Original NDA, 505(b)(2)
2. **SUBMISSION PROVIDES FOR:** Marketing Authorization
3. **MANUFACTURING SITE:**

(b) (4)

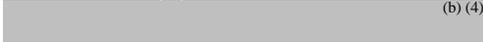


Drug Product:

Hollister-Stier Laboratories LLC
3525 North Regal Street
Spokane, WA 99207-5788
(Establishment Registration No. 3010477)

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Non-sterile liquid nasal spray; intranasal, 15% solution (w/w).
5. **METHOD(S) OF STERILIZATION:** N/A Non-Sterile solution that is

(b) (4)



C. **REMARKS:**

- The Applicant has provided responses to the COMMENTS from Review #1

filename: N022382N000R2.doc

Executive Summary

I. Recommendations

- A. **Recommendation on Approvability** – Recommend Approval
- 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 Applicant provided responses to the initial review to correct the description of the drug process formulation water and has established pre-sterilization bioburden and hold-time criteria.
- B. **Brief Description of Microbiology Deficiencies** – None.
- C. **Assessment of Risk Due to Microbiology Deficiencies** – N/A

III. Administrative

- A. **Reviewer's Signature** _____
Robert Mello, Ph.D.
- B. **Endorsement Block** _____
Bryan S. Riley, Ph.D.
- C. **CC Block**
NDA 22-382

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22382	ORIG-1	ROXRO PHARMA INC	KETOROLAC TROMETHAMINE NASAL SPRAY

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/s/

ROBERT J MELLO
10/02/2009

BRYAN S RILEY
10/02/2009
I concur.

Product Quality Microbiology Review

22 SEPTEMBER 2009

NDA: 22-382/N-000

Drug Product Name

Proprietary: SPRIX

Non-proprietary: Ketorolac Tromethamine Nasal Spray

Review Number: 1

Dates of Submission(s) Covered by this Review

<u>Letter (Submit date)</u>	<u>Stamp (Received Date)</u>	<u>Review Request</u>	<u>Assigned to Reviewer</u>
05 DECEMBER 2008	05 DECEMBER 2008	13 JANUARY 2009	23 JANUARY 2009

Submission History (for amendments only): N/A

Applicant/Sponsor

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bonniehorner@sbcglobal.net

Name of Reviewer: Robert J. Mello, Ph.D.

Conclusion: The application is recommended for approval from microbiology product quality standpoint. Two COMMENTS are provided for the Applicant (see Section 3).

Product Quality Microbiology Data Sheet

- A. 1. **TYPE OF SUBMISSION:** Original NDA, 505(b)(2)
2. **SUBMISSION PROVIDES FOR:** Marketing Authorization
3. **MANUFACTURING SITE:**

(b) (4)

Drug Product:

Hollister-Stier Laboratories LLC
3525 North Regal Street
Spokane, WA 99207-5788
(Establishment Registration No. 3010477)

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Non-sterile liquid nasal spray; intranasal, 15% solution (w/w).
5. **METHOD(S) OF STERILIZATION:** N/A Non-Sterile solution that is
(b) (4)
6. **PHARMACOLOGICAL CATEGORY:** Analgesic
- B. **SUPPORTING/RELATED DOCUMENTS:** None.
- C. **REMARKS:**

- The ONDQA Initial Quality Assessment was filed on 06 MARCH 2009. The drug product is a “low bioburden” nasal solution for limited (one day) use. Suitability of the manufacturing process, which includes (b) (4) processing, specifications and microbiological integrity of the drug substance, drug product for in-use and shelf life duration was identified for consultation to the OPS/NDMS (Microbiology) group. Preservative effectiveness studies were cited as having been performed. Microbial limits specifications and incoming bioburden specifications for the bottle container were cited for consultation to OPS/NDMS.
- The submission was received as a paper desk copy in CTD format.
- There is no Microbiology filing review since the filing meeting was held on January 8, 2009, and the Microbiology consult (dated January 13, 2009) was generated as a result of that filing meeting.
- A summary of a comparability protocol for inclusion of a (b) (4) in the manufacture of the commercial drug product is proposed in the NDA. It will be

(b) (4)

- The solution is a non-sterile liquid produced under (b) (4) to produce a “low bioburden” drug product.
- The submission content follows the July 2002 FDA Guidance "*Nasal Spray and Inhalation Solution, Suspension and Spray Drug Products - Chemistry, Manufacturing and Controls Documentation.*"

Filename: N022382N000R1.doc

Executive Summary

I. Recommendations

- A. Recommendation on Approvability – Recommend Approval**
- 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 a multidose, low-bioburden aqueous solution produced under (b) (4) processing conditions. It is formulated in (b) (4) product is Formulated drug (b) (4). The pump/closure component system is separately (b) (4). The drug product is **not** designated as (b) (4). It does contain (b) (4) disodium edetate but this is listed as a (b) (4). A single final drug product unit is labeled for use as a single daily dose of up to 8 x 0.1ml actuations (sprays)/day. The labeling indicates each unit must be discarded within 24 hours of the initial actuation. Microbial limits testing is included as part of the final product specifications. The applicant provided development study data to support the self-preserving properties of the drug product in excess of the labeled 24 hour dosing regimen per drug product unit (see Section P.2.5, below). The proposed shelf life is 24 months when stored at 2-8°C.

- B. Brief Description of Microbiology Deficiencies – None, but with 2 COMMENTS for the Applicant.**
- C. Assessment of Risk Due to Microbiology Deficiencies – N/A**

III. Administrative

A. Reviewer's Signature _____
Robert Mello, Ph.D.

B. Endorsement Block _____
Bryan S. Riley, Ph.D.

C. CC Block
NDA 22-382

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22382	ORIG-1	ROXRO PHARMA INC	KETOROLAC TROMETHAMINE NASAL SPRAY

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/s/

ROBERT J MELLO
09/23/2009

BRYAN S RILEY
09/23/2009
I concur.