CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202408Orig1s000

CLINICAL MICROBIOLOGY/VIROLOGY REVIEW(S)

Product Quality Microbiology Review

16 JAN 2014

NDA: 202408

Drug Product Name
Proprietary: AVACLYR™ (Acyclovir)
Non-proprietary: Acyclovir Ophthalmic Ointment, 3.0%

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
5/31/2013	5/31/2013	6/06/2013	6/06/2013
6/13/2013	6/13/2013	6/13/2013	6/13/2013
11/27/2013	11/27/2013	11/27/2013	11/27/2013

Applicant/Sponsor
Name: Fera Pharmaceuticals, LLC
Address: 134 Birch Hill Road, Locust Valley, NY 11560

Representative: John D'Angelo
134 Birch Hill Road
Locust Valley, NY 11560

Telephone: 516-277-1449

Name of Reviewer: Neal J. Sweeney, Ph.D.

Conclusion: Recommended for Approval

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: 505 (b) (2) Original NDA

2. SUBMISSION PROVIDES FOR: New drug product

3. MANUFACTURING SITE: (b) (4)

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: Acyclovir (3%) ophthalmic topical multi-dose ointment packaged in 3.5 g tin tubes (b) (4)

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: Antiviral indicated for treatment of herpetic keratitis (dendritic ulcers) in patients with Herpes Simplex Virus (HSV-1 and HSV-2).

B. SUPPORTING/RELATED DOCUMENTS:
ANDA 62-447

C. REMARKS:

The applicant referenced ANDA 62-447 (Erythromycin Ophthalmic Ointment) (b) (4) original sterilization process validation of (b) (4) 3.5 gram tin tubes (b) (4) (b) (4) The original holder of ANDA 62-447 was Altana Pharmaceuticals; however ANDA 62-477 was transferred from Altana to Fera Pharmaceuticals in April 2010. The 3.5 g tin tubes, (b) (4) are identical for both the original Altana product and the proposed Fera product.

Additional CMC information was submitted in the June 13, 2013 and November 27, 2013 amendments and incorporated in this review.

Orphan Drug Designation (ODD# 10-3250) was granted Dec 13, 2013

File name: N202408R1.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability - Recommended for 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 – (b) (4)

B. Brief Description of Microbiology Deficiencies – Based upon the information provided, no microbiology deficiencies were identified.

C. Assessment of Risk Due to Microbiology Deficiencies – N/A

D. Contains Potential Precedent Decision(s)- ☐ **Yes** ☒ **No**
(If yes, provide a brief description and a reference to the page where the precedent is discussed in depth)

III. Administrative

A. Reviewer's Signature _____
Neal J. Sweeney, Ph.D.

B. Endorsement Block _____
Bryan S. Riley, Acting Team Leader

C. CC Block
N/A

Product Quality Microbiology Assessment

1. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q)

MODULE 3.2: BODY OF DATA

S DRUG SUBSTANCE (Review only if the Drug Substance is Sterile, or if other Product Quality Microbiology Issues are involved, see the Drug Product section (P) for detailed guidance)

S.2 Manufacture

S.2.1 Manufacturers

The (b) (4) Acyclovir, USP drug substance is manufactured by (b) (4) Each incoming drug substance lot is tested (b) (4) and microbiological control of the drug substance includes (b) (4)

S.2.2 Description of the Manufacturing Process and Process Controls

The drug product manufacturer (b) (4)

S.2.5 Process Validation and/or Evaluation

Sterilization Validation

(b) (4)

(b) (4)

ADEQUATE

REVIEWER COMMENTS – Drug substance (b) (4) microbiological quality acceptance criteria comply with those specified by USP (b) (4) for pharmaceutical use. Drug substance (b) (4) validation methods and results comply with the FDA Guidance for Industry: Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products.

P DRUG PRODUCT

P.1 Description of the Composition of the Drug Product

- **Description of drug product –** The drug product is a sterile, multi-dose ointment packaged in 3.5 g (b) (4) tin tubes with black LDPE closures.
- **Drug product composition –** Each gram of product contains 30 mg acyclovir, USP and (b) (4) mg white petrolatum, USP.

- **Description of container closure system –**

  The container/closure system that will be used for the commercial drug product is a 3.5 g pre-printed tin tube (b) (4) with a black low density polyethylene cap. The tubes are purchased from (b) (4)

(b) (4)

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

- **Container-Closure and Package integrity -**
  Validation of drug product container/closure (C/C) integrity was demonstrated via microbial challenge by Altana Inc. Pharmaceutical Group, and reported in Validation Study # V-N-0000-16.12, dated October 20, 2003. (b) (4)

(b) (4)

Note: (b) (4)

ADEQUATE

REVIEWER COMMENT – Description of drug product and pharmaceutical development information were consistent with the FDA Guidances for Industry: (1) Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products, and (2) Q8(R2) Pharmaceutical Development.

P.3 Manufacture

P.3.1 Manufacturers

Drug product manufacture, release testing and annual stability testing will all be performed at the following cGMP facility:

(b) (4)

P.3.3 Description of the Manufacturing Process and Process Controls

(b) (4)

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(b) (4)

ADEQUATE

REVIEWER COMMENT – Validation/requalification studies and results were consistent with those delineated in the FDA Guidances for Industry (1) Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products, and (2) Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice, as well as common industry practice.

P.5 Control of Drug Product
P.5.1 Specifications
P.5.2 Analytical Procedures

- Endotoxin – N/A (topical ophthalmic ointment).

- Sterility – Drug product sterility testing is performed USP according to <71> Sterility Test (b) (4) and is included in both the finished product and stability specifications. Validation of the sterility test method was conducted according to (b) (4) protocol (b) (4) and was performed for three different batches (11443, 11470, and 11471) of drug product. (b) (4)

(b) (4)

The USP <71> bacteriostasis/fungistasis requirements were therefore achieved. Validation batches 11443, 11470, and 11471 all passed sterility testing.

ADEQUATE

REVIEWER COMMENT – The drug product specification (sterility) and validations comply with USP <71> Sterility Test, and FDA Guidance for Industry: Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products.

P.7 Container Closure System (description of container closure system if complicated or unusual requiring a more detailed description than provided in P.1) See section P.1

P.8 Stability

P.8.1 Stability Summary and Conclusion

MAINTENANCE OF MICROBIOLOGICAL CONTROL AND QUALITY: STABILITY CONSIDERATIONS

P.8.2 Post-Approval Stability Protocol and Stability Commitment

The applicant commits to placing the first three batches of the drug product on stability testing, and at least one annual batch of each thereafter. According to Stability Protocol (b) (4) sterility testing is to be performed at the 0, 12, 24, and 36 month for the 25ºC/60% RH stability stations. The proposed expiry is (b) (4) months.

P.8.3 Stability Data

Stability data for primary commercial batches (11443, 11470, and 11471)) manufactured at the (b) (4) facility demonstrated that samples passed sterility testing.

ADEQUATE

REVIEWER COMMENT – The submitted stability protocol, commitment and data complies with Guidances for Industry: (1) Q1A(R2) Stability Testing of New Drug Substances and Products, and (2) Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products.

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

None of the components used in manufacture of the drug product has a human or animal origin.

R REGIONAL INFORMATION

R.1 Executed Batch Record

One representative executed batch record (batch 11443) (lots) was provided.

2. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q)
MODULE 1

A. PACKAGE INSERT

The package insert instructions for drug product specify that the drug product intended for topical use only, is applied as (b) (4) The drug product is stored at (b) (4) °C to 25°C.

ADEQUATE

REVIEWER COMMENT – As there are no label instructions for reconstitution/dilution and subsequent storage, no microbial challenge studies are necessary.

3. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS:

(none)

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

/s/

NEAL J SWEENEY
01/22/2014

BRYAN S RILEY
01/23/2014
I concur.