CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203324Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA 203-324

Photrexa (riboflavin 5'-phosphate ophthalmic solution) 0.146% and Photrexa Viscous (riboflavin 5'-phosphate in 20% dextran ophthalmic solution) 0.146%

Avedro, Inc.

George Lunn, Ph.D.
Division of Transplant and Ophthalmology Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 203-324

2. REVIEW #: 2

3. REVIEW DATE: 13-Apr-2016

4. REVIEWER: George Lunn, Ph.D.

5. PREVIOUS DOCUMENTS: None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	16-Sep-2013
Amendment	27-Nov-2013
Amendment	15-Jan-2014
Amendment	21-Jan-2014
Amendment	14-Feb-2014
Amendment	14-Jul-2014
Resubmission	29-Sep-2014
Amendment	14-Nov-2014
Amendment	26-Feb-2015
Amendment	23-Nov-2015
Amendment	09-Feb-2016
Amendment	13-Spr-2016

7. NAME & ADDRESS OF APPLICANT:

Name: Avedro, Inc.

Address:	230 Third Avenue, 5th Floor Waltham, MA 02451
Representative:	Pamela Nelson, Vice-President, Regulatory Affairs
Telephone:	(781) 768-3400

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Photrexa; Photrexa Viscous
b) Non-Proprietary Name (USAN): Riboflavin 5'-phosphate ophthalmic solution 1.46 mg/mL
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION:

10. PHARMACOL. CATEGORY: [redacted] (b) (4)

11. DOSAGE FORM: Ophthalmic solution

12. STRENGTH/POTENCY: 1.200 mg riboflavin per mL (equivalent to 1.46 mg riboflavin 5-phosphate per mL)

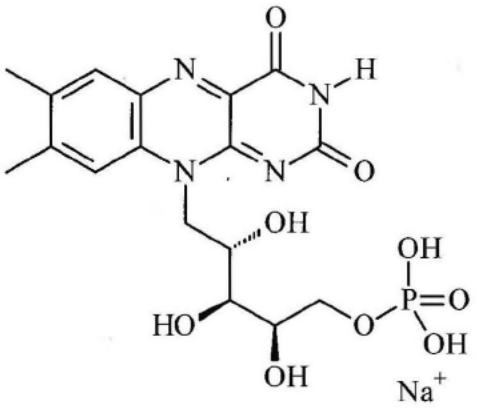
13. ROUTE OF ADMINISTRATION: Topical (ophthalmic)

14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Riboflavin 5'-Phosphate Sodium

Molecular Formula: $C_{17}H_{20}N_4NaO_9P$

Molecular Weight: 478.33

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	Adequate	12/11/15	Reviewed by George Lunn, OPQ
	V			1	Adequate	2/5/14	Reviewed by Denise Miller, Quality Micro
	III				Adequate	1/21/15	Reviewed by Helen Ngai.
	III			1	Adequate	4/1/14	Reviewed by Edwin Jao

(b) (4)	III		(b) (4)	1	Adequate	2/13/14	Reviewed by G. Lunn
	III			1	Adequate	2/11/14	Reviewed by Denise Miller, Quality Micro

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: None

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	Approve	4/11/16	See Panorama
Pharm/Tox	NA		
Biopharm	NA		
LNC	NA		
Methods Validation	Acceptable	4/11/14	Michael Trehy, Division of Pharmaceutical Analysis
OPDRA	NA		
EA	A categorical exclusion is requested and accepted.	10/9/13	G. Lunn
Microbiology	Acceptable - See Quality Micro review	2/18/14	Denise A. Miller

The Chemistry Review for NDA 203-324

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA is recommended for approval from the CMC perspective. All CMC issues concerning the drug substance and the drug product have been satisfactorily resolved. An overall recommendation of Acceptable has been made by the Office of Compliance.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug substance riboflavin 5'-phosphate sodium is manufactured [redacted] (b) (4) [redacted] (b) (4) under DMF [redacted] (b) (4) A Letter of Authorization to reference this DMF is provided. The acceptability of this material for use as a drug substance is based upon a satisfactory review of the DMF. In a review dated 8/23/14 this DMF was found to be adequate. It is noteworthy that the drug substance contains a mixture of riboflavin and various [redacted] (b) (4) species. Information in the literature, however, indicates that free riboflavin generates singlet oxygen (which initiates the cross-linking) with the same efficiency as riboflavin 5'-phosphate and therefore the relative amounts of the various species are not critical.

The drug product solutions contain riboflavin 5'-phosphate sodium, sodium chloride, sodium phosphate monobasic, sodium phosphate dibasic, and sterile water for injection. Photrexa Viscous contains 20% dextran 500 and Photrexa does not. The solutions are [redacted] (b) (4) filled into 3 mL clear glass syringes fitted with a plunger with a rubber stopper and a plastic rigid tip cap.

[redacted] (b) (4) Except for dextran 500 the excipients are compendial. Dextran 500 is a novel excipient. As with other dextrans it is a water-soluble polymer of glucose. There are USP monographs for dextran 1, 40, and 70 and there are EP monographs for dextran 1, 40, 60, and 70. (The number refers to the molecular weight in kiloDaltons.) The

specification for dextran 500 is [redacted] (b) (4), [redacted] acceptable.

From a CMC-perspective, it appears that the formulations used in the clinical trials may not be identical to the proposed commercial formulations. This is ultimately a question for the clinical reviewer.

The drug product is manufactured [redacted] (b) (4) with some testing carried out by outside laboratories. An Overall recommendation of Approve was made by Compliance on 4/11/16. The manufacturing process is described in reasonable detail and the in-process controls are reasonable.

The specification includes tests for appearance, identity, assay, degradants, riboflavin 5'-phosphate, pH, sterility, viscosity, osmolality, particulates, and endotoxins. The specification is acceptable. The analytical methods have been described in reasonable detail and have been validated in an acceptable fashion. The HPLC method has been tested by an FDA laboratory and found to be acceptable. This is the first riboflavin ophthalmic solution to be marketed.

Satisfactory batch analyses are provided for 3 batches of Photrexa and 3 batches of Photrexa Viscous.

The container-closure solution is a 3 mL clear glass syringe fitted with a plunger with a rubber stopper and a plastic rigid tip cap. The syringe is packaged in a Tyvek pouch and this pouch is placed inside a foil pouch. The container-closure system is acceptable.

Thirty months of stability data are provided for three batches of Photrexa Viscous and 24 months of stability data are provided for three batches of Photrexa. Taking into account the stability data the expiration dating period is 18 months.

The applicant requests a categorical exclusion from the requirement to perform an environmental assessment. This request is acceptable.

B. Description of How the Drug Product is Intended to be Used

Photrexa Viscous (riboflavin 5'-phosphate in 20% dextran ophthalmic solution)0.146% and Photrexa (riboflavin 5'-phosphate ophthalmic solution) 0.146% are indicated [redacted] (b) (4) [redacted] The solutions are applied topically to the eye. Riboflavin 5'-phosphate sodium is a photosensitizer and promotes cross-linking in the cornea when irradiated with UV light at 365 nm (3 mW/cm^2) from a UV LED. Normally Photrexa Viscous (containing 20% dextran) is used. However, if corneal thickness is < 400 μm, Photrexa (containing no dextran) is used until the corneal thickness is ≥ 400 μm. Irradiation should not occur until the corneal thickness is ≥ 400 μm.

C. Basis for Approvability or Not-Approval Recommendation

This NDA is recommended for approval from the CMC perspective. All CMC issues concerning the drug substance and the drug product have been satisfactorily resolved. Dr. Denise Miller's Product Quality Microbiology review recommends approval. The composition, manufacturing process, and specifications for the riboflavin 5'-phosphate ophthalmic solutions are appropriate and the expiration dating period of 18 months is supported by adequate data. The container-closure system is appropriate. The labels and labeling are currently under review by the NDA review team. An overall recommendation of Approve has been made by the Office of Compliance.

D. Risk Assessment

Product attribute/ CQA	Risk Mitigation approach in control strategy	Risk Evaluation	Lifecycle Considerations/ Comments
Assay	Protective packaging and storage statement (15-25°C)	Acceptable (M)	Changes in the container-closure system or the storage statement could adversely affect stability. Product is photosensitive
Riboflavin 5'-phosphate level	Drug substance specification	Acceptable (M)	Does not appear to change on stability but only limited information is available. There is evidence that various riboflavin-containing species all function as photosensitizers so conversion to other species may not be a problem.
pH	Controlled during manufacturing process. Solution is buffered.	Acceptable (L)	None
Sterility	Drug product tested for sterility at release and for container-closure integrity on stability	Acceptable (see Quality Micro review)	None
Endotoxins	Drug product tested at release	Acceptable (see Quality Micro review)	None

Viscosity	Controlled during manufacturing process. Viscosity is controlled (b) (4) (b) (4)	Acceptable (L)	Long term degradation (b) (4) on stability may affect the viscosity
Osmolality	Controlled during manufacturing process. Solution is contains buffering salts and sodium chloride (b) (4)	Acceptable (L)	None
Particulates	Tested at release and on stability	Acceptable (M)	Changes to the container-closure system may affect the levels of particulates
Degradants	Tested at release and on stability	Acceptable (M)	Do not appear to change on stability but only limited information is available. There is evidence that various riboflavin-containing species all function as photosensitizers so conversion to other species may not be a problem.
Analytical methods	Validation reports are provided	Acceptable (M)	(b) (4) (b) (4) It is possible that the applicant may propose a (b) (4) method. The associated validation report should be carefully examined as validation has proved to be problematic in the past.
Manufacturing	cGMP controls at facility	Acceptable (M)	This is a sterile product. Manufacturing facilities should continue to have Acceptable ratings

Reviewer's note: This applicant has demonstrated a general lack of competence during the NDA submission process as evidenced by the need to issue a Complete Response Letter with CMC issues in the first review cycle and the numerous Information Requests that were issued. Similar Information Requests were issued during the IND development process and were ignored. Eventually the application was found to be satisfactory. Future reviewers are advised to carefully scrutinize any supplements submitted to this NDA. The applicant has committed to only extending the expiration dating period by means of a Prior Approval Supplement. In addition future reviewers are advised to consult Section II.A Labeling & Package Insert for a discussion of nomenclature issues and how they may affect future generic versions.

III. Administrative

A. Reviewer's Signature

George Lunn, Ph.D.

George Lunn -S

Digitally signed by George Lunn -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=George Lunn -S, 0.9.2342.19200300.100.1.1=1300120718
Date: 2016.04.13 10:52:17 -04'00'

B. Endorsement Block

Balajee Shanmugam, Ph.D., Acting Branch Chief

C. CC Block

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance, Division of Manufacturing and Quality
Abdominal and Surgical Devices Branch

DATE:	**January 15, 2014**
TO:	George Lunn, Division of New Drug Quality Assessment II, Center for Drug Evaluation and Research, WO-22, Room 1444 george.lunn@fda.hhs.gov
Cc:	Office of combination products at combination@fda.gov
THRU:	Ronald L. Swann, Chief, Abdominal and Surgical Devices Branch, Division of Manufacturing and Quality, Office of Compliance, CDRH, WO-66, Room 3534 Ronald L. Swann -S 2014.02.04 12:56:11 -05'00'
FROM:	Felicia Brayboy, CSO, Abdominal and Surgical Devices Branch, Division of Manufacturing and Quality, Office of Compliance, CDRH, WO-66, Room 3547
Applicant:	Avedro Inc. 230 Third Avenue, 5th floor Waltham MA, 02451
Application #	NDA-203324
Product Name:	(b) (4) KXL System
CONSULT INSTRUCTIONS:	Evaluate the use of the KXL device for use with the proposed riboflavin ophthalmic solution and identify any developmental studies the sponsor should conduct with this device/formulation combination. There is a device facility associated with this application that should be inspected (see attached on Page 6 of the 356 form).

The Office of Compliance at CDRH received a consult request from CDER regarding (b) (4) (b) (4) KXL device, NDA 203324. The consult indicated that there is a device facility

associated with this application that should be inspected. CDRH evaluated the need for an inspection at the Avedro facility. Additionally, CDRH Office of Compliance reviewed the manufacturing information provided in the application.

Product Description

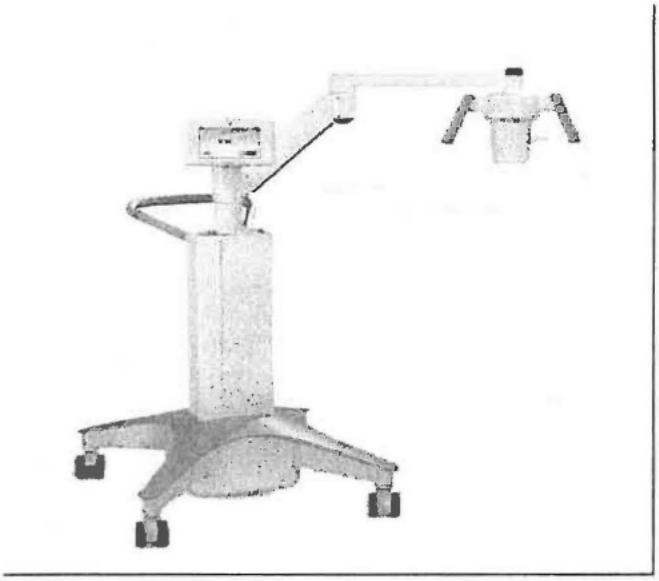
Corneal collagen cross-linking is a procedure that uses UVA light and a photosensitizer (riboflavin) to improve the biomechanical properties of the cornea by strengthening the corneal tissue in the anterior stroma.

The KXL System is an electronic medical device that delivers ultraviolet light (365 nm wavelength) in a circular pattern onto the cornea after application of Photrexa or Photrexa (b)(4) (riboflavin ophthalmic solution). Irradiating the Photrexa or Photrexa (b)(4) creates radical riboflavin and singlet oxygen, which forms intermolecular bonds in corneal collagen, stiffening the cornea through crosslinking. UV flux and irradiation time (that is, fluence) at the cornea are controlled by an onboard computer system.

The KXL System is portable with an articulating arm to allow movement of the system for alignment of the UV Beam to the patient's cornea. An internal battery powers the system; the battery is recharged by a system internal charger from any standard AC outlet. The treatment parameters (induction period, UV power and UV energy) are selected through the user interface touch screen computer.

Avedro's riboflavin ophthalmic solutions, Photrexa and Photrexa (b)(4), are sterile, phosphate buffered saline solutions containing 0.12% riboflavin (Vitamin B2) in either 20% dextran or 0% dextran, respectively. The drug products are supplied as pre-filled 3-mL Type I glass syringe packaged in a sealed secondary light-block pouch. Riboflavin, a water-soluble vitamin, is an essential nutrient and a natural component of many foods. It is considered to be non-toxic and Generally Recognized as Safe (GRAS).

Figure 1: Overview Illustration of the KXL System



Application documents evaluation

The application was searched for documents pertaining to applicable 21 CFR part 820 regulations for this combination product. Information found in the Regional Information/Deice Information section (3.2.R Regional Information/Device Information/Device Information Appendices) of the application was reviewed (Management Controls, Design Controls, Corrective and Preventive Actions and Production & Process Controls). The information provided appeared adequate. This information was also reviewed as part of an inspection conducted in May of 2012 (see below).

Regulatory history evaluation

After reviewing the application, the applicant, Avedro Inc. (FEI# 3007851054), was identified as a facility subjected to applicable Medical Device Regulations under 21 CFR part 820.

An analysis of the firm's inspection history over the past 2 years showed that an inspection under the Medical Device regulation was conducted on May 21, 2012 – May 25, 2012 and was classified Voluntary Action Indicated (VAI). This was a routine pre-announced QSIT Level II [Comprehensive] inspection performed per FACTS Assignment # 1324480 and in accordance with CP 7382.845, Inspection of Medical Device Manufacturers. The firm is a Class II Medical Device Manufacturer who also imports for export, a drug product used with one of its devices. The two devices made by the company were for sale only outside of the United States at the time of the inspection. This was the firm's initial FDA inspection.

The four major QSIT subsystems were covered during the inspection: Management

Controls, Design Controls, Corrective and Preventive Actions (CAPA) and Production & Process Controls. Products covered included mainly the KXL System with the (b) (4) riboflavin drug. Review of Standard Operating Procedures and records related to the following include: CAPA, complaint and investigation, complaint and CAPA logs, incoming inspection, device history, supplier evaluation, training, and information related to internal audits and management reviews.

At the close of the inspection, an FDA 483 was issued for the following objectionable conditions:

(b) (4)

Avedro, Inc. sent a written response to the FDA 483, dated June 14, 2012, which addressed all three observations. Per FACTS, the response was adequate but required verification.

Deficiencies to be conveyed to the applicant

There are no deficiencies to be relayed to the applicant.

CDRH Recommendation

Upon review of the documentation provided, CDRH/OC is requesting no additional information from the applicant in order to complete the review of the application to ascertain compliance with the applicable 21 CFR part 820 regulations.

CDRH will concur with CDER's decision regarding NDA-203324 approval. NDA-203324 is approvable from the perspective of the Medical Device Regulations. The desk review of the application for compliance with the Medical Device Regulations showed no deficiencies. However, a post-market inspection is recommended for Avedro Inc., 230 Third Avenue, 5th floor, Waltham MA, 02451 (FEI# 3007851054). This inspection should be coordinated by CDER. The EIR should be assigned to CDER and then sent to CDRH as a consult for review. This inspection is being recommended because Avedro, Inc. sent a written response to the FDA 483 (issued for the May 2012 inspection), dated June 14, 2012, which addressed all three observations. Per FACTS, the response was adequate but required verification. Additionally, since the applicant intends to now market the

product in the United States, a follow up inspection at the site with the KXL device as the subject is appropriate.

Felicia L. Brayboy
2014.02.04 14:34:02 -05'00'

Felicia L. Brayboy

Prepared/typed: FBrayboy: January 14, 2014
Reviewed/approved: RSwann: 02/04/14
Reviewed/approved:

CTS No.: ICC1300555

NDA-203324

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

/s/

JACQUELYN E SMITH
03/25/2015

NDA 203-324

Photrexa (riboflavin phosphates ophthalmic solution) and Photrexa Viscous (riboflavin phosphates ophthalmic solution) 20% dextran

Avedro, Inc.

George Lunn, Ph.D.
Division of Transplant and Ophthalmology Products

Table of Contents

APPEARS THIS WAY ON ORIGINAL

Chemistry Review Data Sheet

1. NDA 203-324

2. REVIEW #: 2

3. REVIEW DATE: 04-Mar-2015

4. REVIEWER: George Lunn, Ph.D.

5. PREVIOUS DOCUMENTS: None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	16-Sep-2013
Amendment	27-Nov-2013
Amendment	15-Jan-2014
Amendment	21-Jan-2014
Amendment	14-Feb-2014
Amendment	14-Jul-2014
Resubmission	29-Sep-2014
Amendment	14-Nov-2014
Amendment	26-Feb-2015

7. NAME & ADDRESS OF APPLICANT:

Name:	Avedro, Inc.
Address:	230 Third Avenue, 5th Floor Waltham, MA 02451

Representative:	Pamela Nelson, Vice-President, Regulatory Affairs
Telephone:	(781) 768-3400

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Photrexa; Photrexa Viscous
b) Non-Proprietary Name (USAN): Riboflavin phosphates ophthalmic solution 1.46 mg/mL
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION:

10. PHARMACOL. CATEGORY: (b) (4)

11. DOSAGE FORM: Ophthalmic solution

12. STRENGTH/POTENCY: 1.200 mg riboflavin per mL (equivalent to 1.46 mg riboflavin phosphates per mL)

13. ROUTE OF ADMINISTRATION: Topical (ophthalmic)

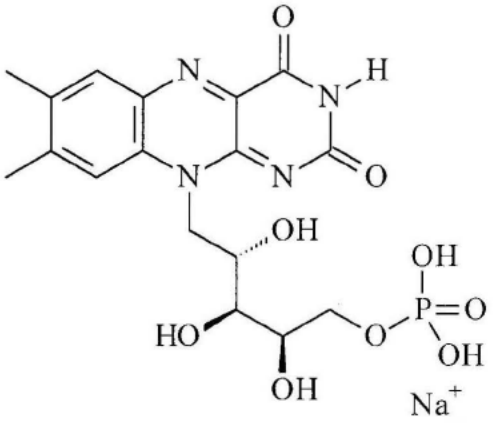
14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Riboflavin 5'-Phosphate Sodium

Molecular Formula: $C_{17}H_{20}N_4NaO_9P$

Molecular Weight: 478.33

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	Adequate	8/23/14	Reviewed by George Lunn, ONDQA
	V			1	Adequate	2/5/14	Reviewed by Denise Miller, Quality Micro
	III				Adequate	1/21/15	Reviewed by Helen Ngai.
	III			1	Adequate	4/1/14	Reviewed by Edwin Jao
	III			1	Adequate	2/13/14	Reviewed by G. Lunn

(b) (4)			(b) (4)				
	III			1	Adequate	2/11/14	Reviewed by Denise Miller, Quality Micro

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: None

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	Approve	2/17/15	Linda Ng
Pharm/Tox	NA		
Biopharm	NA		
LNC	NA		
Methods Validation	Acceptable	4/11/14	Michael Trehy, Division of Pharmaceutical Analysis
OPDRA	NA		
EA	A categorical exclusion is requested and accepted.	10/9/13	G. Lunn
Microbiology	Acceptable - See Quality Micro review	2/18/14	Denise A. Miller

The Chemistry Review for NDA 203-324

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA is recommended for approval from the CMC perspective. All CMC issues concerning the drug substance and the drug product have been satisfactorily resolved. An overall recommendation of Acceptable has been made by the Office of Compliance.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug substance riboflavin 5'-phosphate sodium is manufactured [redacted] (b) (4) [redacted] (b) (4) under DMF [redacted] (b) (4). A Letter of Authorization to reference this DMF is provided. The acceptability of this material for use as a drug substance is based upon a satisfactory review of the DMF. In a review dated 8/23/14 this DMF was found to be adequate. It is noteworthy that the drug substance contains a mixture of riboflavin and various [redacted] (b) (4) species. Information in the literature, however, indicates that free riboflavin generates singlet oxygen (which initiates the cross-linking) with the same efficiency as riboflavin 5'-phosphate and therefore the relative amounts of the various species are not critical.

The drug product solutions contain riboflavin 5'-phosphate sodium, sodium chloride, sodium phosphate monobasic, sodium phosphate dibasic, and sterile water for injection. Photrexa Viscous contains 20% dextran 500 and Photrexa does not. The solutions are [redacted] (b) (4) filled into 3 mL clear glass syringes fitted with a plunger with a rubber stopper and a plastic rigid tip cap.

[redacted] (b) (4) Except for dextran 500 the excipients are compendial. Dextran 500 is a novel excipient. As with other dextrans it is a water-soluble polymer of glucose. There are USP monographs for dextran 1, 40, and 70 and there are EP monographs for dextran 1, 40, 60, and 70. (The number refers to the molecular weight in kiloDaltons.) The

specification for dextran 500 is [redacted] (b) (4) acceptable.

From a CMC-perspective, it appears that the formulations used in the clinical trials may not be identical to the proposed commercial formulations. This is ultimately a question for the clinical reviewer.

The drug product is manufactured [redacted] (b) (4) with some testing carried out by outside laboratories. An Overall recommendation of Approve has been made by Compliance. The Overall Re-evaluation Date is 4/4/16. The manufacturing process is described in reasonable detail and the in-process controls are reasonable.

The specification includes tests for appearance, identity, assay, degradants, riboflavin 5'-phosphate, pH, sterility, viscosity, osmolality, particulates, and endotoxins. The specification is acceptable. The analytical methods have been described in reasonable detail and have been validated in an acceptable fashion. The HPLC method has been tested by an FDA laboratory and found to be acceptable. This is the first riboflavin ophthalmic solution to be marketed.

Satisfactory batch analyses are provided for 3 batches of Photrexa and 3 batches of Photrexa Viscous.

The container-closure solution is a 3 mL clear glass syringe fitted with a plunger with a rubber stopper and a plastic rigid tip cap. The syringe is packaged in a Tyvek pouch and this pouch is placed inside a foil pouch. The container-closure system is acceptable.

Twelve months of satisfactory stability data are provided for three batches of each formulation. The expiration dating period is 18 months.

The applicant requests a categorical exclusion from the requirement to perform an environmental assessment. This request is acceptable.

B. Description of How the Drug Product is Intended to be Used

Photrexa Viscous (riboflavin phosphates ophthalmic solution 1.46 mg/mL) with 20% dextran and Photrexa (riboflavin phosphates ophthalmic solution 1.46 mg/mL) are indicated [redacted] (b) (4) The solutions are applied topically to the eye. Riboflavin 5'-phosphate sodium is a photosensitizer and promotes cross-linking in the cornea when irradiated with UV light at 365 nm (3 mW/cm^2) from a UV LED. Normally Photrexa Viscous (containing 20% dextran) is used. However, if corneal thickness is < 400 μm Photrexa (containing no dextran) is used until the corneal thickness is ≥ 400 μm. Irradiation should not occur until the corneal thickness is ≥ 400 μm.

C. Basis for Approvability or Not-Approval Recommendation

This NDA is recommended for approval from the CMC perspective. All CMC issues concerning the drug substance and the drug product have been satisfactorily resolved. Dr. Denise Miller's Product Quality Microbiology review recommends approval. The composition, manufacturing process, and specifications for the riboflavin phosphates ophthalmic solutions are appropriate and the expiration dating period of 18 months is supported by adequate data. The container-closure system is appropriate. The labels and labeling are currently under review by the NDA review team. An overall recommendation of Acceptable has been made by the Office of Compliance.

D. Risk Assessment

Product attribute/ CQA	Risk Mitigation approach in control strategy	Risk Evaluation	Lifecycle Considerations/ Comments
Assay	Protective packaging and storage statement (15-25°C)	Acceptable (M)	Changes in the container-closure system or the storage statement could adversely affect stability. Product is photosensitive
Riboflavin 5'-phosphate level	Drug substance specification	Acceptable (M)	Does not appear to change on stability but only limited information is available. There is evidence that various riboflavin-containing species all function as photosensitizers so conversion to other species may not be a problem.
pH	Controlled during manufacturing process. Solution is buffered.	Acceptable (L)	None
Sterility	Drug product tested for sterility at release and for container-closure integrity on stability	Acceptable (see Quality Micro review)	None
Endotoxins	Drug product tested at release	Acceptable (see Quality Micro review)	None
Viscosity	Controlled during	Acceptable	Long term degradation (b) (4) on

	manufacturing process. Viscosity is controlled [redacted] (b) (4)	(L)	stability may affect the viscosity
Osmolality	Controlled during manufacturing process. Solution is contains buffering salts and sodium chloride [redacted] (b) (4)	Acceptable (L)	None
Particulates	Tested at release and on stability	Acceptable (M)	Changes to the container-closure system may affect the levels of particulates
Degradants	Tested at release and on stability	Acceptable (M)	Do not appear to change on stability but only limited information is available. There is evidence that various riboflavin-containing species all function as photosensitizers so conversion to other species may not be a problem.
Analytical methods	Validation reports are provided	Acceptable (M)	[redacted] (b) (4) [redacted] (b) (4) It is possible that the applicant may propose a [redacted] (b) (4) method. The associated validation report should be carefully examined as validation has proved to be problematic in the past.
Manufacturing	cGMP controls at facility	Acceptable (M)	This is a sterile product. Manufacturing facilities should continue to have Acceptable ratings

Reviewer's note: This applicant has demonstrated a general lack of competence during the NDA submission process as evidenced by the need to issue a Complete Response Letter in the first review cycle and the numerous Information Requests that were issued. Similar Information Requests were issued during the IND development process. Eventually the application was found to be satisfactory. Future reviewers are advised to carefully scrutinize any supplements submitted to this NDA.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

George Lunn, Ph.D.: Same date as draft review
Anamitro Banerjee, Ph.D., CMC lead
Dorota Matecka, Ph.D., Acting Branch Chief

C. CC Block

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(b) (4)

[redacted]

George Lunn -A

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Date: 2015.03.05 08:32:56 -05'00'

Dorota M. Matecka -S

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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300123291, cn=Dorota M. Matecka -S
Date: 2015.03.05 09:12:01 -05'00'

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date March 5, 2014

From Linda Ng, Ph.D.,
Division of Good Manufacturing Practice Assessment
Office of Manufacturing & Product Quality

Subject Concurrence with (b) (4) District Office ((b) (4)-DO) Withhold Recommendation for NDA 203-324, Riboflavin Ophthalmic Solution, 0.12%

Thru Mahesh Ramanadham, Acting Branch Chief
New Drug Manufacturing Assessment Branch
Division of Good Manufacturing Practice Assessment

To Rapti Madurawe, Branch Chief
Branch V
Division of New Drug Quality Assessment II

To Caryn McNab, Pre-Approval Manager
ORA/(b) (4) District Office

Applicant: Avedro Inc
230 3rd Ave 5th floor
Waltham, MA 02451

Manufacturer: (b) (4)

The Division of Good Manufacturing Practice Assessment (DGMPA) has completed a review of an establishment inspection report (EIR) covering a pre-approval inspection (PAI) and GMP inspection conducted by (b) (4) District ((b) (4)-DO) (b) (4) at the (b) (4) (b) (4) facility. This site is listed as the (b) (4) drug product manufacturer in support of this NDA. DGMPA has also reviewed the firm's (b) (4) written response to the 483 observations. This inspection was initiated by (b) (4)-DO to provide pre-approval coverage for NDA 203-324. According to (b) (4)-DO, the inspection was initially classified OAI for NDA specific coverage with a withhold recommendation. After an evaluation of the firm's response (b) (4)-DO re-affirmed their withhold recommendation.

After review of the firm's response, DGMPA concurs with the (b) (4)-DO's withhold recommendation for the (b) (4) facility. (b) (4)-DO recommended withholding approval of this application due to product specific deficiencies. The FDA Form-483 included twelve observations with the first two to be the most significant, product specific observations. Since these are also reviewed in the application, the reviewer, George Lunn, Ph.D., was asked if such information has been received or reviewed.

The reviewer confirmed that the information received so far is inadequate. More data are expected to come in an amendment by March 28, 2014. This is past the PDUFA date of March 16, 2014. Until the data are received and evaluated to be adequate, the deficiencies are still outstanding and impact application action.

The following discussion highlights the first observation specific to NDA 203-324, Riboflavin Ophthalmic Solution, 0.12%.

(b) (4)

[redacted]

(b) (4)

CDER/OMPQ/DGMPA evaluation of firm's response: (b) (4) The firm commits to generate and submit the data once the reports are completed. The March 28, 2014 amendment is expected to contain the information.

(b) (4)

The data have not been submitted either to the District or to the review division. Neither the investigator nor the CMC reviewer finds this satisfactory. Until the information is submitted and evaluated to be acceptable (b) (4) this is deficient.

Conclusion: Response is still outstanding.

Product specific and general CGMP observations and response evaluation:

(b) (4)

(b) (4)

The recommended language for incorporation in the CR letter is as follows:

During a recent inspection of the (b) (4) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

If you have any questions, please contact me at (301) 796-1426 or by email at linda.ng@fda.hhs.gov.

cc:
CMS #72601
Balajee Shanmugam, Ph.D., CMC Lead, OPS/ONDQA/DNDQAII
George Lunn, CMC Reviewer, OPS/ONDQA/DNDQAII/BRV
William Boyd, M.D., Clinical Team Leader, OND/DTOP

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/s/

LINDA L NG
03/05/2014

MAHESH R RAMANADHAM
03/05/2014

NDA 203-324

Photrexa (riboflavin phosphates ophthalmic solution)

Avedro, Inc.

George Lunn, Ph.D.
Division of Transplant and Ophthalmology Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 203-324

2. REVIEW #: 1

3. REVIEW DATE: 19-Feb-2014

4. REVIEWER: George Lunn, Ph.D.

5. PREVIOUS DOCUMENTS: None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	16-Sep-2013
Amendment	27-Nov-2013
Amendment	15-Jan-2014
Amendment	21-Jan-2014
Amendment	14-Feb-2014

7. NAME & ADDRESS OF APPLICANT:

Name:	Avedro, Inc.
Address:	230 Third Avenue, 5th Floor Waltham, MA 02451
Representative:	Pamela Nelson, Vice-President, Regulatory Affairs
Telephone:	(781) 768-3400

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Photrexa; Photrexa (b) (4)
b) Non-Proprietary Name (USAN): Riboflavin phosphates ophthalmic solution 1.46 mg/g
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION:

10. PHARMACOL. CATEGORY: (b) (4)

11. DOSAGE FORM: Ophthalmic solution

12. STRENGTH/POTENCY: 1.46 mg/g

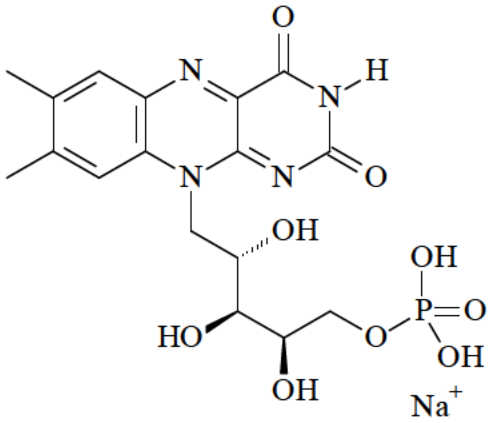
13. ROUTE OF ADMINISTRATION: Topical (ophthalmic)

14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Riboflavin 5'-Phosphate Sodium

Molecular Formula: $C_{17}H_{20}N_4NaO_9P$

Molecular Weight: 478.33

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	Pending			Outstanding issues still require resolution
	V			1	Adequate	2/5/14	Reviewed by Denise Miller, Quality Micro
	III			1	Adequate	1/17/14	Reviewed by Lakshmi Narasimhan
	III			1	Adequate	6/6/11	Reviewed by Josephine Jee
	III			1	Adequate	2/13/14	Reviewed by G. Lunn

(b) (4)	III		(b) (4)	1	Adequate	2/11/14	Reviewed by Denise Miller, Quality Micro

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: None

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	Pending	10/23/13	
Pharm/Tox	NA		
Biopharm	NA		
LNC	NA		
Methods Validation	Pending		
OPDRA	NA		
EA	A categorical exclusion is requested and accepted.	10/9/13	G. Lunn
Microbiology	Acceptable - See Quality Micro review	2/18/14	Denise A. Miller

The Chemistry Review for NDA 203-324

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA is not recommended for approval from the CMC perspective, please refer to Section II.C.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug substance riboflavin 5'-phosphate sodium is manufactured [redacted] (b) (4) under DMF [redacted] (b) (4) A Letter of Authorization to reference this DMF is provided. The acceptability of this material for use as a drug substance is based upon a satisfactory review of the DMF. At the current time this DMF has unresolved deficiencies. It is noteworthy that the drug substance contains a mixture of riboflavin and various [redacted] (b) (4) species. Information in the literature, however, indicates that free riboflavin generates singlet oxygen (which initiates the cross-linking) with the same efficiency as riboflavin 5'-phosphate and therefore the relative amounts of the various species are not critical.

The drug product solutions contain riboflavin 5'-phosphate sodium, sodium chloride, sodium phosphate monobasic, sodium phosphate dibasic, and sterile water for injection. Photrexa contains 20% dextran 500 and Photrexa [redacted] (b) (4) does not. The solutions are [redacted] (b) (4) filled into 3 mL clear glass syringes fitted with a plunger with a rubber stopper and a plastic rigid tip cap.

[redacted] (b) (4) Except for dextran 500 the excipients are compendial. Dextran 500 is a novel excipient. As with other dextrans it is a water-soluble polymer of glucose. There are USP monographs for dextran 1, 40, and 70 and there are EP monographs for dextran 1, 40, 60, and 70. (The number refers to the molecular weight in kiloDaltons.) The specification for dextran 500 is [redacted] (b) (4) [redacted] (b) (4) acceptable.

From a CMC-perspective, it appears that the formulations used in the clinical trials may not be identical to the proposed commercial formulations. This is ultimately a question for the clinical reviewer.

The drug product is manufactured [redacted] (b) (4) with some testing carried out by outside laboratories. The Overall Recommendation from EES is Pending. All sites are acceptable except for the drug product manufacturer, [redacted] (b) (4) Following an inspection a 483 was issued and the District Office currently recommends withhold for this site. The manufacturing process is described in reasonable detail and the in-process controls are reasonable.

The specification includes tests for appearance, identity, assay, degradants, riboflavin 5'-phosphate, pH, sterility, viscosity, osmolality, particulates, and endotoxins. The specification is not adequate for a number of reasons. The validation of the HPLC method is not adequate. The HPLC method will be tested by an FDA laboratory. This is the first riboflavin ophthalmic solution to be marketed.

Unsatisfactory batch analyses are provided for 3 batches of Photrexa and 3 batches of Photrexa [redacted] (b) (4)

The container-closure solution is a 3 mL clear glass syringe fitted with a plunger with a rubber stopper and a plastic rigid tip cap. The syringe is packaged in a Tyvek pouch and this pouch is placed inside a foil pouch. The container-closure system is acceptable.

Six months of stability data are provided for three batches of each formulation. For a number of reasons these data are not adequate.

The sponsor requests a categorical exclusion from the requirement to perform an environmental assessment under 21 CFR 25.31.

B. Description of How the Drug Product is Intended to be Used

Photrexa (riboflavin phosphates ophthalmic solution 1.46 mg/g) with 20% dextran and Photrexa [redacted] (b) (4) (riboflavin phosphates ophthalmic solution 1.46 mg/g) are indicated [redacted] (b) (4)

The solutions are applied topically to the eye. Riboflavin 5'-phosphate sodium is a photosensitizer and promotes cross-linking in the cornea when irradiated with UV light at 365 nm (3 mW/cm^2) from a UV LED. Normally Photrexa (containing 20% dextran) is used. However, if corneal thickness is < 400 µm Photrexa [redacted] (b) (4) (containing no dextran) is used until the corneal thickness is ≥ 400 µm. Irradiation should not occur until the corneal thickness is ≥ 400 µm.

C. Basis for Approvability or Not-Approval Recommendation

This NDA is not recommended for approval from the CMC perspective. There are numerous outstanding deficiencies. A brief list follows.

- An Overall Recommendation of Acceptable has not been made by Compliance. The District Office currently recommends Withhold for the drug product manufacturing site.
- The validation of the HPLC method is not adequate
- The drug product specification is not adequate. The drug product specification should include tests for degradants (specified, unspecified, and total) and appropriate acceptance criteria should be proposed.
- The stability data cannot be evaluated without an appropriate drug product specification.
- There are unresolved labeling issues. The non-proprietary name should be changed to riboflavin phosphates and the label claim should be 1.46 mg/g.
- DMF (b) (4) is currently inadequate. An official response to the Agency Deficiency letter dated 2/7/14 has not been received although the company has agreed to incorporate the Agency recommendations.
- The device has been reviewed by CDRH and deficiencies were communicated to the applicant on 2/11/14.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

George Lunn, Ph.D.: Same date as draft review
Balajee Shanmugam, Ph.D., CMC lead
Rapti Madurawe, Ph.D., Branch Chief

C. CC Block

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/s/

GEORGE LUNN
02/20/2014
This application is not recommended for review from the CMC perspective.

BALAJEE SHANMUGAM
02/20/2014

RAPTI D MADURAWE
02/20/2014

Product Quality Microbiology Review

13 February 2014

NDA: 203-324/N000

Drug Product Name
Proprietary: Photrexa
Non-proprietary: riboflavin ophthalmic solution (20% dextran)

Proprietary: Photrexa (b) (4)
Non-proprietary: riboflavin ophthalmic solution (0% dextran)

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
16 September 2013	16 September 2013	16 September 2013	16 September 2013

Submission History (for 2nd Reviews or higher) – NA

Applicant/Sponsor
Name: Avedro
Address: 230 Third Avenue
Waltham MA 02451
Representative: Pamela Nelson
Telephone: (781) 768-3430

Name of Reviewer: Denise A. Miller

Conclusion: Recommend to approve

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Resubmission of Original application

2. SUBMISSION PROVIDES FOR: Manufacture of a topical ophthalmic drug solution to be used with an ultraviolet device following refractive surgery.

3. MANUFACTURING SITE:
(b) (4)

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

- Dosage Form: Sterile solution in a prefilled 3 mL syringe
- Route of Administration: topical ophthalmic
- Strength/Potency: 0.12%

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

6. PHARMACOLOGICAL CATEGORY: ophthalmic solution

B. SUPPORTING/RELATED DOCUMENTS:

DMF (b) (4): (b) (4): LOA dated (b) (4) for DMF submission of 31 October 2013.

(b) (4)

NDMS review D00501_2013OCT31_A1.docx: Adequate

DMF (b) (4): (b) (4) LOA dated (b) (4) to reference the entire DMF. NDMS review F (b) (4)_2013SEPT04_A1.docx concluded that the DMF was adequate.

DFM (b) (4): (b) (4) LOA dated (b) (4) for the entire DMF. NDMS review D (b) (4)_2012DEC14_A1.docx conclusion was adequate.

C. REMARKS:

The application is a resubmission following a Refuse to File (RTF). This eCTD formatted resubmission addressed the quality microbiology issues cited in the RTF letter.

filename: N203324N000R1.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability – Recommendation to be approved from a quality microbiology perspective.

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

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – This is a sterile ophthalmic solution that is (b) (4) filled into single use syringes for a topical application of the drug product.

B. Brief Description of Microbiology Deficiencies – None identified in the information provided.

C. Assessment of Risk Due to Microbiology Deficiencies – NA

D. Contains Potential Precedent Decision(s)- ☐ **Yes** ☒ **No**

III. Administrative

A. Reviewer's Signature _____
Denise A. Miller
Microbiologist, OPS/NDMS

B. Endorsement Block_____
Bryan S. Riley, Ph.D.
Senior Microbiologist, OPS/NDMS

C. CC Block
N/A

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/s/

DENISE A MILLER
02/18/2014

BRYAN S RILEY
02/18/2014
I concur.