CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210913Orig1s000

PRODUCT QUALITY REVIEW(S)

QUALITY ASSESSMENT

Recommendation: Approval

NDA 210913
Review # 1
Jul 19, 2018

Drug Name/Dosage Form	***Cequa (cyclosporine) ophthalmic solution***
Strength	*0.09%*
Route of Administration	*Topical ophthalmic*
Rx/OTC Dispensed	*Rx*
Applicant	*Sun Pharma Global FZE*
US agent, if applicable	*NA*

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Original	*10/16/2017*
Amendment	*11/13/2017*
Amendment	*12/12/2017*
Amendment	*12/22/2017*
Amendment	*1/26/2018*
Amendment	*3/22/2018*
Amendment	*3/29/2018*
Amendment	*4/5/2018*
Amendment	*4/10/2018*
Amendment	*5/1/2018*
Amendment	*6/14/2018*

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Application Technical Lead	Chunchun Zhang	NA
Drug Substance	Monica Cooper	Charles Jewell
Drug Product	Milton Sloan	Thomas Oliver
Microbiology	Jason Morgan	John Metcalfe
Biopharmaceutics	Gerlie Gieser	Jing Li
Process	Nancy Waites	Maotang Zhou
Facility	Khalid Khan	Ying Zhang
Regulatory Business Process Manager	Kristine Leahy	NA
ORA Lead	Caryn McNabb	NA

QUALITY ASSESSMENT

Laboratory (OTR)	NA	NA
Environmental Assessment (EA)	Milton Sloan	Thomas Oliver

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status[1]	Date Review Completed	Comments
(b) (4)	Type II	(b) (4)	(b) (4)	Adequate	8/18/2017	LoA: 10/2/2017 Reviewed by Siba Bhattacharyya
(b) (4)	Type III	(b) (4)	(b) (4)	NA		LoA: 6/20/2017
	Type III			NA		LoA

[1]NA (There is enough data in the application, therefore the DMF did not need to be reviewed).

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	118954	This product during IND development

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	NA			
Pharmacology/Toxicology	Adequate		4/9/2018	Aaron Ruhland
CDRH	NA			
Clinical	NA			
Other	NA			

Executive Summary

I. Recommendations and Conclusion on Approvability

NDA 210913, as amended, has provided sufficient product quality information to assure the identity, strength, purity, and quality of the proposed drug product Cequa (cyclosporine) ophthalmic solution. All information requests and review issues have been addressed.

The Office of Process and Facilities has issued an overall acceptable recommendation for all the facilities on 5/9/2018.

Therefore, NDA 210913 is recommended for approval from Product Quality perspective.

Labeling recommendations from the Product Quality perspective will be provided to the OND PM for consideration during final labeling discussion.

II. Summary of Quality Assessments

A. Product Overview

Proposed Indication(s) including Intended Patient Population	For the treatment of increasing tear production (b) (4) (b) (4) associated with keratoconjunctivitis sicca (dry eyes).
Duration of Treatment	Instill one drop twice daily into each eye using a single use container. See package insert for the recommended dosage in patients.
Maximum Daily Dose	As above (see the package insert for details).
Alternative Methods of Administration	NA

B. Quality Assessment Overview

i. Drug Substance Quality Summary

The drug substance, cyclosporine, is a white to almost white odorless powder. It is manufactured by (b) (4) The drug substance referenced in DMF (b) (4) was found adequate by Siba Bhattacharyya on 8/18/2017.

ii. Drug Product Quality Summary

Cequa (cyclosporine) ophthalmic solution, 0.09 % is indicated to increase tear production [redacted] of keratoconjunctivitis sicca (dry eye). The drug product is provided in a single-use 0.9 mL [redacted] vial with 0.25 mL fill through [redacted]. The applicant has defined the OTX-101 drug product as an ophthalmic solution in a nanomicelle formulation containing cyclosporine, which was found acceptable by the review team, OTR-technical report, and OPQ Policy group, refer to the drug product review section for the detailed discussion. Formulation bridging data per se are not needed because only one formulation was used throughout development. A biowaiver request was not requested nor required. The PK, efficacy and safety of the proposed to-be-marketed drug product was investigated in clinical trials.

All excipients used in the formulation are adequately qualified. No novel excipients are used in the formulation. The drug product specification includes tests for appearance, two non-specific identification tests by HPLC and FT-IR, assay, impurities (specified, unspecified and total), pH, osmolality, viscosity, sterility, micelle size determination, particulate matter, uniformity of dosage units and weight loss. Evaluation of the risk assessment of the elemental impurities was performed and indicates the results are lower than the permitted daily exposure (PDE) as noted in USP<232> and the ICH Q3D guidance. The proposed specification is acceptable to ensure quality of the product over its expiration period. All analytical methods are described in reasonable detail and have been adequately validated.

The proposed commercial scale is [redacted]. Batch analyses are provided for 3 registration batches on scales of [redacted] and [redacted] and manufactured in the commercial site Laboratoire Unither. All batches complied with the proposed specification.

Drug product stability data is available to 18 months at long term storage 25°C/40%RH and 12 months at 30°C/65%RH for three registration batches. Minor trends are observed in the data on storage up to 12 and 18 months. The attributes are within proposed specifications. The shelf life of 24 months when stored at 20°C-25°C is granted. Per the agency's request, the applicant submitted the post approval commitment that include a statement to withdraw from the market if any lot where quality tests indicate the distributed lots do not conform to the approved specifications for the drug product on 7/17/2018.

The storage statement is "Store at 20°C to 25°C (68°F to 77°F)"] and will be finalized at the OND's labeling meeting.

The proposed drug product manufacturing process consists of [redacted]. During the NDA review several information requests regarding to in-process controls, [redacted],

environmental monitoring methods and (b) (4) validations etc were conveyed to and addressed by the applicant. The overall information regarding the manufacturing process provided in the NDA submission and subsequent amendments was found acceptable.

All the facilities are acceptable based on the profile. No pre-approval inspection is required at this review cycle. Therefore, the overall recommendation of "Approve" was entered for the NDA into Panorama by OPF on 5/9/2018. Post approval inspection for (b) (4) (b) (4) (b) (4) refer to the facility review chapter for the detailed discussion.

C. Special Product Quality Labeling Recommendations (NDA only)

NA

D. Final Risk Assessment (see Attachment)

I. From Initial Risk Identification			Review Assessment		
Attribute/CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Eval.	Lifecycle Considerations Comments
Sterility	Formulation Container closure[1] Process parameters Scale/equipment Site[3]	H	Sterilization has been validated.	L	Post-approval stability protocol[2] will test sterility.
Endotoxin Pyrogen	Formulation Container closure[1] Process parameters Scale/equipment	L	This is a topical product and therefore does not require testing for endotoxin.	L	No endotoxin testing required.
Assay (API), stability	Formulation Container closure[1] Raw materials	L	Robust analytical method validated for assay; no trend on stability; levels remain within the proposed specification. Label claim will be delivered.	L	

Assay (preservative)	Formulation Container closure[1] Process parameters Scale/equipment	**L**	No preservative is used as it is a single use vial.	**L**	
Uniformity of Dose (Fill Vol/ Deliverable volume)	Formulation Container closure[1] Process parameters Scale/equipment	**M**	0.9 mL (b) (4) vial with (b) (4) mL fill volume.	**L**	
pH	Formulation Container closure[1] Process parameters Scale/equipment	**L**	(b) (4); No trend on stability observed. Impact on other quality attributes is very minimal.	**L**	
Particulate matter	Formulation Container closure[1] Process parameters Scale/equipment	M	Per ophthalmic product requirements, particulate matter is controlled in the drug specification per USP <789>.	L	

[1]Stability studies demonstrate container closure compatibility with the drug product for all quality attributes.

MICROBIOLOGY

Product Background:

NDA: 210913

Drug Product Name / Strength: Cyclosporin Ophthalmic Solution, 0.09%

Route of Administration: Topical ocular; ophthalmic

Applicant Name: Sun Pharma Global FZE
PO Box #122304, Office #43, Block Y, SAIF Zone
Sharjah, U.A.E
E-mail Address: vishwanath.kenkare@sunpharma.com

Authorized Agent: Jeffrey Yuan, Associate VP,
Global Regulatory Affairs, Sun Pharmaceuticals Industries, Inc.
2 Independence Way
Princeton, NJ, 08540
Phone: 609-720-5326
E-mail Address: jeff.yuan@sunpharma.com

Manufacturing Site: Laboratoire Unither
ZI de la Guerie
F-50211 Coutances Cedex, France
FEI: 3006974616

Method of Sterilization: The drug product is sterilized by (b) (4) (b) (4)

Review Recommendation: Recommended for approval from the standpoint of product quality microbiology.

***Review Summary*:** The drug product is supplied as a package of six (6) sealed polyfoil aluminum pouches, each containing two (2) cards of five (5) single-use 0.9 ml (b) (4) (b) (4) vials containing 0.25 ml of 0.09% Cyclosporin Ophthalmic Solution.

List Submissions Being Reviewed: 10/16/2017; 01/26/2018; 04/10/2018; 06/14/2018

Highlight Key Outstanding Issues from Last Cycle: None

Remarks: This submission was provided in the eCTD format.

Concise Description Outstanding Issues Remaining: See the review summary.

Supporting Documents: N/A

List Number of Comparability Protocols (ANDA only): N/A

S Drug Substance

The drug substance, Cyclosporine, USP (b) (4) (b) (4)

P.1 Description of the Composition of the Drug Product

- ***Description of drug product*** – Cyclosporine Ophthalmic Solution, 0.09% is a sterile, unit-dose, non-preserved clear, colorless ophthalmic solution containing cyclosporine solubilized nanomicelles; each vial contains a 0.25 ml in a 0.9 ml (b) (4) (b) (4) vial.

- ***Drug product composition*** – The drug product is composed of Cyclosporine, Polyoxyl (b) (4) Hydrogenated Castor Oil, Octoxynol-40, Sodium Phosphate Monobasic Dihydrate, Sodium Phosphate Dibasic Anhydrous, (b) (4), Polyvinylpyrrolidine, Hydrochloric Acid, Sodium Hydroxide, and Water for Injection. Additional information regarding the product composition, as derived from Section 3.2.P.1, in the Description and Composition of the Drug Product, is as follows:

Component	Pharmacopoeial Reference	Function	g/ml
Cyclosporine	USP	Active Ingredient	0.0009 g
Polyoxyl (b) (4) Hydrogenated Castor Oil	USP/NF	(b) (4)	
Octoxynol-40	-		
Sodium Phosphate Monobasic Dihydrate	USP/NF		
Sodium Phosphate Dibasic Anhydrous	USP/NF		
(b) (4)	USP/NF		
Polyvinylpyrrolidone	USP/NF		
Hydrochloric Acid	USP/NF	QA to Adjust pH	
Sodium Hydroxide	USP/NF	QA to Adjust pH	
Water for Injection	USP/NF	(b) (4)	

- ***Description of container closure system*** – Cyclosporine Ophthalmic Solution, 0.09% is supplied as a single-use 0.9 ml (b) (4) vial with a 0.25 ml fill. The drug product is supplied as a package of six (6) sealed polyfoil aluminum pouches, each containing two (2) cards of five (5) vials. A summary of the drug product container closure system components is as follows:

Component	Material	Description	Manufacturer/Supplier	DMF #
0.9 ml Unit Dose Vial	(b) (4) (b) (4) used for (b) (4) vial	(b) (4)		(b) (4)

Reviewer's Assessment: ***Acceptable***

- The description of the drug product composition and container/closure system is adequate.

P.2 Pharmaceutical Development
P.2.5 Microbiological Attributes

Container/Closure and Package Integrity

(b) (4)

An information request was sent to the applicant, dated 12/08/2017, and a response was received 01/26/2018. The following information was requested:

1) *The (b) (4) test of (b) (4) vials in Section 3.2.P.3, Pharmaceutical Development is acknowledged; however, insufficient detail was provided. For more information, please refer to the Agency's 1994 "Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products"; see section IV (G). To facilitate review of the application, please provide a summary of the methods and results demonstrating the integrity of the microbiological barrier of the (b) (4) vial container-closure system, to include testing performed for initial validation. The sensitivity of the method used for container-closure integrity testing should be specified and provided.*

The applicant responses are summarized as follows:
Microbial Immersion Test: As part of the response to the information request, the applicant provided the results from a microbial immersion container closure integrity test validation study in Section 3.2.P.2, Verification of the Container Closure Integrity by

(b) (4)

Acceptance criteria were defined as:

- All media utilized supports the growth of *B. diminuta*
- Positive controls are positive
- Negative controls are negative
- All test units are negative; if any are positive, an identification is performed to confirm the presence of *B. diminuta*

The results of the microbial immersion test are summarized as follows:

Parameter	Acceptance Criteria	Observation
Date of Test	-	8/14/2015
Organism Used	*Brevundimonas diminuta*	*Brevundimonas diminuta*
Organism Population (CFU/ml)	NLT (b) (4)	(b) (4)
Incubation Condition	30±2°C	30±2°C
Test Vial Results	Shall Show No Growth	No Growth
Negative Control Vials	Shall Show No Growth	No Growth
Positive Control Vials	Shall Show Growth	Growth

(b) (4)

An information request was sent to the applicant, dated 03/13/2018, and a response was received 04/10/2018. The following information was requested:

(b) (4)

(b) (4)

The applicant responses are summarized as follows:

(b) (4)

An information request was sent to the applicant, dated 04/28/2018, and a response was received 06/14/2018. The following information was requested:

(b) (4)

(b) (4)

[redacted]

Reviewer's Assessment: ***Acceptable***

- The applicant's verification of container closure integrity is consistent with regulatory expectations for a sterile pharmaceutical product.

Antimicrobial Effectiveness Testing

The drug product is a single use vial; no AET is required.

Reviewer's Assessment: ***Not Applicable***

P.3 Manufacture
P.3.1 Manufacturers

Drug Product:

Laboratoire Unither
ZI de la Guerie
F-50211 Coutances Cedex, France

P. 3.3 Description of the Manufacturing Process and Process Controls

OVERALL MANUFACTURING OPERATION
(*Section 3.2.P.3, Description of Manufacturing Process and Process Controls*)

(b) (4)

[redacted]

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Reviewer's Assessment: ***Acceptable***

- The applicant has provided adequate descriptions of the manufacturing facility and equipment used in the manufacturing of commercial batches and the manufacturing process is consistent with regulatory expectations for a sterile pharmaceutical product.

Sterilization/Depyrogenation of containers, closures, equipment and Components – See P.3.5

Reviewer's Assessment: ***Not Applicable***

ENVIRONMENTAL MONITORING

(b) (4)

(b) (4)

Component Bioburden

The applicant established specification for the drug substance is ≤ (b) (4) CFU/g for TAMC (b) (4) CFU/g TYMC (tested per USP <61>). The action level for the (b) (4) is (b) (4) CFU/g. A summary of the drug product component microbiological limits is as follows:

Component	TAMC	TYMC	Test Method
Cyclosporine	(b) (4)		USP<61>
Octoxynol-40			USP<61>/<62>
Polyoxyl (b) (4) Hydrogenated Castor Oil			Ph.Eur. 2.6.12
Sodium Phosphate Monobasic, Dihydrate			-
Sodium Phosphate Dibasic, Anhydrous			Ph.Eur.
(b) (4)			
Polyvinylpyrrolidone			Ph.Eur. 2.6.12
Hydrochloric Acid			Ph.Eur.
Sodium Hydroxide			-
WFI			USP
(b) (4)			-

An information request was sent to the applicant, dated 12/08/2017, and a response was received 01/26/2018. The following information was requested:

1) *The description of the specification concerning media fills and environmental monitoring in Section 3.2.P.3, Manufacture, is acknowledged; however, insufficient detail was provided. For more information, please refer to the Agency's 1994 "Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products"; see section IV (D, E, and F). To facilitate review of the application, please provide:*

   c. *For environmental monitoring, a description of the sites monitored; alert and action level specifications (to include, but not limited to, air, inanimate surfaces, personnel, and water); the microbiological materials and methods used; the routine monitoring methods used for yeasts, molds, and anaerobes; and a description of the actions taken when specifications are exceeded.*

The applicant responses are summarized as follows:

1.c) The applicant provided a description of environmental monitoring in Section 1.11.1, Quality Response to Request for Information – Microbiology, pgs. 10-14.

(b) (4)

The environmental monitoring alert and action levels for filling are summarized as follows (*copied from Section 1.11.1, "Quality Response to Request for Information – Microbiology", pg. 13*):

(b) (4)

(b) (4)

An information request was sent to the applicant, dated 03/13/2018, and a response was received 04/10/2018. The following information was requested:

1) *The description of the environmental monitoring methods in Section 1.11.1, "Quality Response to Request for Information – Microbiology", pgs. 10-14, is acknowledged; however, additional information is required. For environmental monitoring of*

21 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

Reviewer's Assessment: ***Acceptable***

P.5 Control of Drug Product

P. 5.1 Specification

The product release specification includes the following microbiological test:

Test	Acceptance Criterion	Method
Sterility	No evidence of microbial Growth	USP<71>

Reviewer's Assessment: ***Acceptable***

- The applicant has met regulatory expectations for the product release specification.

P.5.2 Analytical Procedures

Reviewer's Assessment: See section P.5.1 and P.5.3

P.5.3 Validation of Analytical Procedures

Endotoxins

The drug product is a sterile ophthalmic solution; as such, it has no requirement for an endotoxins specification.

Reviewer's Assessment: ***Not Applicable***

Sterility
(*Section 3.2.P.5.3, Test for Sterility validation report*)

Test Method: Equivalent to USP<71>
Acceptance Criteria: No evidence of microbial growth

The sterility test verification was performed using the Steritest sterility testing device (Millipore). Bacteriostasis and fungistasis testing was performed to demonstrate no interference between the drug product and the test microorganisms, to include: *Staphylococcus aureus* (ATCC 6538), *Pseudomonas aeruginosa* (ATCC 9027), *Clostridium sporogenes* (ATCC 19404), *Bacillus subtilis* (ATCC 6633), *Candida albicans* (ATCC 10231), and *Aspergillus brasiliensis* (ATCC 16404). (b) (4)

(b) (4)

The following lot of drug product was used for the sterility test method verification: CSAU-1323-L07.

Reviewer's Assessment: ***Acceptable***

- The applicant has met regulatory expectations with regard to the test method, acceptance criteria and verification of the suitability of use of the sterility test that will be performed on the drug product prior to its release.

Bioburden Test
(*Section 3.2.P.3.5, Validation of the membrane filtration method Ph Eur 2612 – English*)

Test Method: In-house
Acceptance Criteria: < (b) (4) CFU/ (b) (4) ml

An information request was sent to the applicant, dated 12/08/2017, and a response was received 01/26/2018. The following information was requested:

1) *The description of the bioburden acceptance criteria for* (b) (4) *bioburden in Section 3.2.P.3.4 is acknowledged; however, other than a reference to an "in-house" method, no information was provided regarding the bioburden testing methodology to*

demonstrate that it is equivalent to, or better than, the requirements established in USP<61>. Please provide a summary of the validation data for the (b) (4) (b) (4) *bioburden testing method.*

The applicant responses are summarized as follows:

1) The clarified that the bioburden method was conducted per Ph.Eur. 2.6.12, which is harmonized with USP<61>. A copy of the method verification report was included in Section 3.2.P.3.5, "*Validation of the membrane filtration method Ph Eur 2612 – English*", and microbial recovery was confirmed in the presence and absence of the drug product using *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Bacillus subtilis*, *Candida albicans*, and *Aspergillus brasiliensis*.

Reviewer's Assessment: ***Acceptable***

P.7 Container Closure

Summary table of the container closure system proposed

Reviewer's Assessment: See section P.1.

P.8 Stability

P. 8.1 Stability Summary and Conclusion

The proposed expiry is 24 months. Stability samples were tested at the initial time point, and then again after storage at 25°C/40% RH and 30°C/65% RH for 12 months; all results met the acceptance criteria for sterility.

Reviewer's Assessment: ***Acceptable***

- The applicant's proposed 24 month expiry is acceptable based on the provided microbial test data.

P. 8.2 Post-Approval Stability Protocol and Stability Commitment

The product stability specification includes the following microbiological test:

Test	Acceptance Criteria	Method
Sterility	No evidence of microbial Growth	USP<71>

Post-approval stability conditions will be 25±2°C/40±5% RH for at least 36 months, and 30±2°C/65±5% RH for at least 12 months. The testing schedule in the post-approval protocol is as follows:

Test Schedule for Initial Commercial Stability Batches								
36 months, 25±2°C/40±5% RH								
Interval (Month)	**0**	**3**	**6**	**9**	**12**	**18**	**24**	**36**
Sterility	X	-	-	-	X	-	X	X

Test Schedule for Initial Commercial Stability					
12 months, 30±2°C/65±5% RH					
Interval (Month)	**0**	**3**	**6**	**9**	**12**
Sterility	X	-	-	-	X

The applicant committed to initiate and conduct post-approval stability studies on the first three commercial production batches, with the results of the testing to be submitted as part of routine annual reporting. If additional data beyond the expiry, on at least three production batches, support extension of the expiration period, the expiration may be extended and the data will be filed in an annual report.

Reviewer's Assessment: ***Acceptable***

- The applicant has met regulatory expectations with regard to the design of the stability testing program to support the drug product's microbiological quality throughout its shelf life.

P.8.3 Stability Data

The applicant provided sterility data up to 12 months.

Reviewer's Assessment: ***Acceptable***

- The applicant provided acceptable microbiology stability data.

A Appendices

A.2 Adventitious Agents Safety Evaluation

Reviewer's Assessment: ***Acceptable***

- ***See Section A.2.1 below.***

A.2.1 Materials of Biological Origin

(*Section 2.3.A, Adventitious Agents Safety Evaluation*)

The drug product is [redacted] (b) (4)

[redacted] (b) (4)

[redacted] (b) (4) No viral or non-viral adventitious agents are used in, or introduced during, the manufacture of the drug substance.

Reviewer's Assessment: ***Acceptable***

A.2.2 Testing at Appropriate Stages of Production

Reviewer's Assessment: ***Not Applicable***

A.2.3. Viral Testing of Unprocessed Bulk

Reviewer's Assessment: ***Not Applicable***

A. 2.4 Viral Clearance Studies

Reviewer's Assessment: ***Not Applicable***

R Regional Information

Executed Batch Records

Executed batches: CSAU-1323-L12, CSAU-1323-L16, and CSAU-1323-L17

The batch records generally confirm that validated sterilization and [redacted] (b) (4) processes were used for the manufacture of the exhibit batches.

Reviewer's Assessment: ***Acceptable***

- The applicant has met the regulatory expectations regarding the executed batch records.

Comparability Protocols

Reviewer's Assessment: ***Not Applicable***

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

2.A. Package Insert

Maximum dose: The recommended dose of the drug product is one drop twice daily (approximately 12 hours apart) into each eye using a single-use container. No specified volume is indicated for a single drop.
Storage: 20 - 25°C
Description: Cyclosporine Ophthalmic Solution, 0.09%, is packaged in sterile, preservative-free single-use vials. Each vial contains 0.25 ml filled into a 0.9 ml (b) (4) container; 10 vials are packaged into a polyfoil aluminum pouch, and 6 pouches are packaged into a box. There is no dilution or reconstitution step.

Reviewer's Assessment: ***Acceptable***

- The applicant has met regulatory expectations regarding the information related to issues of product quality microbiology provided in the product labeling.

Post-Approval Commitments: See P.8.2

Reviewer's Assessment: ***Not Applicable***

List of Deficiencies: N/A

***Primary Microbiology Reviewer Name and Date*:** Jason K. Morgan, Ph.D., 06/18/2018

***Secondary Reviewer Name and Date*:** John W. Metcalfe, Ph.D.; 06/20/2018

Jason Morgan

Digitally signed by Jason Morgan
Date: 6/20/2018 02:32:35PM
GUID: 573cb41f005b429215eef443f34949a3

John Metcalfe

Digitally signed by John Metcalfe
Date: 6/21/2018 08:31:56AM
GUID: 503451f000004f68b7145543c615dbba
Comments: I concur with the primary reviewer's assessment.

6 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Chunchun Zhang

Digitally signed by Chunchun Zhang
Date: 7/19/2018 10:57:31AM
GUID: 51269608000064178e75377202fe6c5d