

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207986Orig1s000

CHEMISTRY REVIEW(S)



Recommendation:
NDA: Approval

NDA 207986
Review #1
Nov 5, 2015

Drug Name/Dosage Form	Ciprofloxacin 6% Otic Suspension
Strength	1 mL/vial (single patient use vial)
Route of Administration	Injection
Rx/OTC Dispensed	Rx
Applicant	Otonomy, Inc
US agent, if applicable	NA

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original-SD1	Feb. 25, 2015	All disciplines
Amendment-SD2	Apr. 24, 2015	Drug product, biopharmaceutics, quality micro
Amendment-SD4	May 28, 2015	Drug product, process
Amendment-SD6	Jul. 24, 2015	Drug product, process
Amendment-SD7	Aug. 7, 2015	Drug product
Amendment-SD10	Sep. 23, 2015	Biopharmaceutics
Amendment-SD12	Oct. 5, 2015	Quality micro
Amendment-SD13	Oct. 15, 2015	Biopharmaceutics
Amendment-SD14	Oct. 20, 2015	Drug product
Amendment-SD15	Oct. 28, 2015	Biopharmaceutics
Amendment-SD16	Nov. 02, 2015	Biopharmaceutics
Amendment-SD17	Nov. 03, 2015	Biopharmaceutics

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Haripada Sarker	ONDP/DNDAPI/Branch I
Drug Product	Chunchun Zhang	ONDP/DNDP-1/Branch III
Process	Kumar Janoria	OPF/DPAIII/PABVII
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Facility	Quallyna Porte	OPF/BII
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Regulatory Business Process Manager	Navi Bhandari	OPRO/DRBPMI/RBPMBI
Application Technical Lead	Chunchun Zhang	ONDP/DNDAPI/Branch I
Laboratory (OTR)	NA	NA
ORA Lead	Paul Perdue Jr.	OMPTO/DMPTPO/MDTP
Environmental Assessment (EA)	Chunchun Zhang	ONDP/DNDP-1/Branch III

Table of Contents

Table of Contents	2
Quality Review Data Sheet	3
Executive Summary	5
Primary Quality Review	10
ASSESSMENT OF THE DRUG SUBSTANCE	10
2.3.S DRUG SUBSTANCE	10
ASSESSMENT OF THE DRUG PRODUCT	23
2.3.P DRUG PRODUCT	23
R.2 Comparability Protocols.....	56
ASSESSMENT OF THE PROCESS.....	58
2.3.P DRUG PRODUCT	58
R.2 Comparability Protocols.....	83
ASSESSMENT OF THE FACILITIES	
2.3.S DRUG SUBSTANCE.....	83
2.3.P DRUG PRODUCT	85
ASSESSMENT OF THE BIOPHARMACEUTICS INFORMATION	89
ASSESSMENT OF MICROBIOLOGY.....	107
ASSESSMENT OF ENVIRONMENTAL ANALYSIS	126
I. Review of Common Technical Document-Quality (Ctd-Q) Module 1	127
Labeling & Package Insert.....	127
II. List of Deficiencies To Be Communicated.....	137

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCE D	STATUS ¹	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type II	(b) (4)	Drug substance: Ciprofloxacin anhydrate manufacturing, testing, packaging, storage and shipping	Adequate	Oct 6, 2015 by Haripada Sarker	LoA: Sep 15, 2014.
	Type II	(b) (4)	(b) (4)	Adequate	NA	LoA: Oct 13, 2014
	Type II	(b) (4)	(b) (4)	Adequate	No review needed. No new amendment after prior review by Libaniel Rodriguez on Jan 20, 2015.	LoA: Sep 1, 2014
	Type III	(b) (4)	(b) (4)	Adequate	Oct 20, 2015 by Chunchun Zhang	LoA: Feb 25, 2015.
	Type III	(b) (4)	(b) (4)	N/A		LoA: Sep 17, 2014.
	Type V	(b) (4)	(b) (4)	Adequate	10/1/2014 by Dr. Denise Miller	LoA: Feb 25, 2015.

¹Adequate, Adequate with Information Request, Deficient, or N/A (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
RLD	NDA 019537	Cipro tablets
IND	IND 110244	This product during IND development

2. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	NA			
Pharmacology/Toxicology	Adequate		Oct 13, 2015	James Wild
CDRH	NA			
Clinical	Adequate		Oct 6, 2015	Mark Needles, Tom Smith
Other	NA			

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 207986 is recommended for approval from the Product Quality perspective. CMC-related labeling recommendations have been provided to the OND PM for consideration during final labeling review.

1. Summary of Complete Response issues Not applicable
2. Action letter language, related to critical issues such as expiration date
 - “An expiration dating period of 30 months is approved for Ciprofloxacin suspension when packaged and stored as described in the attached labeling.”
3. Benefit/Risk Considerations
Evaluation of the quality aspects of Ciprofloxacin suspension supports approval without consideration of specific benefit/risk aspects.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable. None

II. Summary of Quality Assessments

A. Drug Substance [Ciprofloxacin] Quality Summary

The drug substance, ciprofloxacin will be supplied by two suppliers, (a) (b)(4) (under DMF (b)(4)) and (b) (b)(4) (under DMF (b)(4)). Both DMF's were previously reviewed for other NDAs/ANDAs, and were found to be adequate. No new significant CMC update for drug substance is noted in the NDA or in the corresponding Type-2 DMFs ((b)(4)). Ciprofloxacin USP has been utilized as reference standard in the DMFs to justify the drug substance quality. For further details, see DMFs ((b)(4)) and detailed review notes, below.

B. Drug Product [Ciprofloxacin Otic Suspension] Quality Summary

The drug product consists of ciprofloxacin otic suspension 6% (60 mg/mL, w/v) packaged in 2 mL, USP Type I glass vials with a 13 mm neck finish, a 13 mm (b)(4) stopper, and a 13 mm aluminum seal with plastic flip-off top. The applicant's claim for extended-release was denied. Please see biopharmaceutics review for details.

6. Container Closure: 2 mL, USP Type I glass vials with a 13 mm neck finish, a 13 mm (b) (4) stopper, and a 13 mm aluminum seal with plastic flip-off top.
7. Expiration Date & Storage Conditions: 30 months with the storage statement of stored at 2–8°C (36–46°F).
8. List of co-packaged components: None

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Otiprio
Non Proprietary Name of the Drug Product	Ciprofloxacin suspension
Non Proprietary Name of the Drug Substance	Ciprofloxacin
Proposed Indication(s) including Intended Patient Population	Treatment of middle ear effusion in pediatric patients with otitis media undergoing tympanostomy tube placement.
Duration of Treatment	One single administration
Maximum Daily Dose	0.1 mL per affected ear
Alternative Methods of Administration	None

D. Biopharmaceutics Considerations

1. BCS Designation:

The Applicant did not make any claim for BCS classification.

2. Biowaivers/Biostudies

- Biowaiver Requests

The Applicant’s request for a waiver of in vivo bioavailability studies is granted based on the following justifications:

- a. The proposed drug product is intended for local action therefore systemic blood levels are not representative of the efficacy. The Applicant demonstrated the efficacy of the proposed drug product in two Phase 3 studies (201-201302 and 201-201303) in pediatric patients.
- b. Based on the literature data, it is estimated that the ciprofloxacin plasma C_{max} after oral administration of a single dose of 250 mg ciprofloxacin (tablet) is approximately 570-fold higher than the C_{max} after otic administration of 0.84 mg ciprodex (solution) after a single dose. These findings indicate that the expected systemic exposure after otic administration of the proposed drug product is very low.

- PK studies

The Applicant did not conduct any human PK studies for this proposed product.

- IVIVC

There is no IVIVC established for this product

E. Novel Approaches None

F. Any Special Product Quality Labeling Recommendations None

G. Process/Facility Quality Summary

See detailed Risk Assessment Tables for Drug Substance and Drug Product Facilities in review notes, below.

H. Life Cycle Knowledge Information

From Initial Risk Identification			Review Assessment		
Attribute/CQA	Factors that can impact the CQA	Initial Risk Ranking*	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations and Comments
Appearance	Particle size	L	Monitored at release and stability	Acceptable (L)	Product is reasonably stable. Only obvious trend The only obvious trend is higher (b) (4) content with time and temperature.
Assay	Mixing temp	L	Monitored at release and stability	Acceptable (L)	
Impurities/degradation products including leachables and extractables	Drug substance assay; mixing temp (b) (4)	L	Monitored at release and stability	Acceptable (L)	
Content uniformity	Particle size	M	Demonstrate through in-process control	Acceptable (L)	
Dissolution	Particle size Viscosity Formulation	M	Optimized validated dissolution method	Acceptable (L)	The original dissolution method was optimized to reduce variability. Although the optimized dissolution method does not discriminate for particle size and viscosity, these attributes are controlled via other methods. The dissolution acceptance criterion was (b) (4) from Q=(b) (4) % at 60 minutes to Q=(b) (4) % at 60 minutes. The dissolution method is used as a quality control tool.
pH	Amount of HCl (b) (4)	L	Monitored at release and stability	Acceptable (L)	
Osmolality	(b) (4) content; viscosity formulation	L	Monitored at release and stability	Acceptable (L)	
Bacterial Endotoxins	Drug substance, sterilization process	S		Acceptable (L)	
Sterility	Sterilization process	S		Acceptable (L)	

*Risk ranking applies to product attribute/CQA

**For example, critical controls, underlying control strategies assumptions, post marketing commitment, knowledge management post approval, etc.

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead Signature:

This NDA is recommended for approval from the Product Quality perspective.

Chunchun Zhang -S

Digitally signed by Chunchun Zhang -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People,
cn=Chunchun Zhang -S, 0.9.2342.19200300.100.1.1=2001178137
Date: 2015.11.05 12:11:34 -05'00'

Chunchun Zhang, Ph.D.; CMC reviewer; Branch 3; Division of New Drug Products I

Branch Chief Signature:

I concur with Dr. Chunchun Zhang's recommendation.

**Balajee
Shanmugam -S**

Digitally signed by Balajee Shanmugam -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=1300217143,
email=Balajee.Shanmugam -S,
Date: 2015.11.05 11:41:24 -05'00'

Balajee Shanmugam, Ph.D.; Acting Branch Chief; Branch 3; Division of New Drug Products I

Primary Quality Review

ASSESSMENT OF THE DRUG SUBSTANCE

2.3.S DRUG SUBSTANCE (DS)

2.3.S.1 General Information

This 505(b)(2) NDA is for Drug product, OTO-201, a sterile, preservative-free otic suspension of 6% (60 mg/mL, w/v) ciprofloxacin in a neutral pH buffered, isotonic solution containing a mucoadhesive glycol polymer, poloxamer 407. The LD for this NDA 207986 is NDA 19537 (Cipro Tablet).

The drug substance, ciprofloxacin will be supplied by two suppliers, (a) (b)(4) (under MF (b)(4)) and (b) (b)(4) (under MF (b)(4)). Both the drug substance related MFs (Master Files) were previously reviewed for NDA/ANDA, and were found to be adequate. No new significant CMC update for drug substance is noted in the NDA or in the corresponding Type-2 MFs ((b)(4)). Ciprofloxacin USP has been utilized as reference standard in the MFs to justify the DS quality. The MF (b)(4), (Review-9 and 10) is found to be adequate.

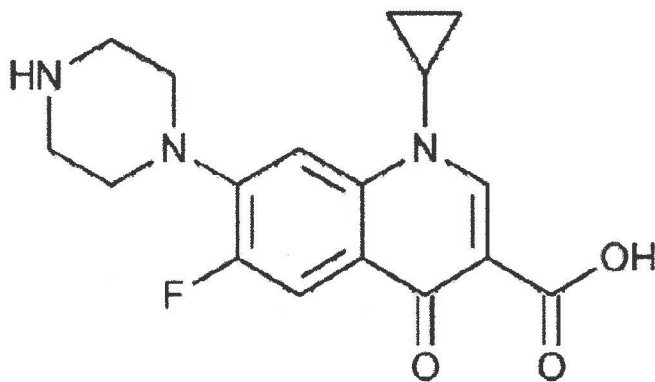
The DS (ciprofloxacin) information from both the MFs (b)(4) are summarized in this NDA 207986 as following.

DS Information in the NDA submission.

Name/Structure:

Chemical Name: Ciprofloxacin

Molecular Structure:



General Properties of Ciprofloxacin

Table 1.

Physical/Chemical Properties	Description
Description	White (b) (4) powder, (b) (4).
Solubility	Practically insoluble in water. Very slightly soluble in ethanol and methylene chloride
pH of 1.0% solution	(b) (4)
Polymorphism	No polymorphic forms are reported
Isomerism	There are no asymmetric centers in the molecule, therefore ciprofloxacin does not exhibit any isomerism

Solubility of ciprofloxacin in buffers of different pH was determined. All buffers were prepared at (b) (4) concentration. The highest solubility of ciprofloxacin is observed around pH (b) (4) in the buffers tested. Ciprofloxacin has very limited solubility around pH (b) (4)

Also see MF (b) (4) (specifically review #8) and MF (b) (4) (specifically review #5) reviews.

Reviewer's Assessment: Adequate to support the NDA.

2.3.S.2 Manufacture

S.2.1 Manufacturer



(b) (4)

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OVERALL ASSESSMENT AND SIGNATURES: DRUG SUBSTANCE

Reviewer's Assessment and Signature: From Drug Substance perspective, the NDA 207-986 is found to be acceptable based on information provided in reference MF (b) (4) and MF (b) (4). See MF (b) (4) and MF (b) (4) reviews in DARRTS.

Haripada Sarker

Date: 10-07-2015

Supervisor Comments and Concurrence: I concur.

**Kasturi Srinivasachar
Acting Branch Chief, Div. of New Drug API, ONDP
10-07-2015**

ASSESSMENT OF THE DRUG PRODUCT

2.3.P DRUG PRODUCT

2.3.P.1 Description and Composition of the Drug Product

Parameters*	Reference Product (NDA 19537)	Product under Review
<i>Type</i>	Cipro®Ciprofloxacin Hydrochloride Tablet 250 mg	Ciprofloxacin otic suspension 1mL/vial
<i>Description</i>	Nearly white to slightly yellowish coated round tablet	Sterile, single-patient use Ciprofloxacin suspension in buffered Poloxamer 407 solution for injection
<i>Target Weight</i>	(b) (4) mg/tablet	1mL (60 mg/mL)
<i>Dimensions/Size</i>	100/bottle	1mL/vial
<i>Container/Closure Design</i>	Plastic bottle 120 mL HDPE white square (b) (4) packaging	A clear 2 mL Type I glass vial with an (b) (4) stopper and aluminum seal with plastic flip-off top
<i>Excipients (not in RLD) which require label warning</i>	NA	NA

1. Are there any scientific or regulatory concerns about the proposed composition of the drug product?

Applicant's Response:

The drug product Ciprofloxacin otic suspension provided as 1 mL/vial is a sterile, single patient use suspension of ciprofloxacin USP in buffered poloxamer 407 solution. The

drug product is filled and packed in a clear 2 mL Type I glass vial with an (b) (4) stopper and aluminum seal with plastic flip-off top.

A list of all components of the Ciprofloxacin suspension, 1 mL/vial with their amounts, functions and reference to their quality standard is summarized in the table below:

Ingredient	Quality Standard	Function	% w/w	Composition (mg/mL)
Ciprofloxacin	USP	Active ingredient	(b) (4)	60
Poloxamer 407	NF	(b) (4)	(b) (4)	(b) (4)
Sodium Chloride	USP			
Tromethamine	USP			
Hydrochloric Acid	NF			
Water for Injection (WFI)	USP			
Total				

Reviewer's Assessment:

Adequate. The components and composition of Ciprofloxacin suspension have been adequately identified. The range of Poloxamer 407 at (b) (4)% is found acceptable by the Pharm/Tox reviewer, Dr. James Wild (email communication dated on Apr. 16, 2015).

2.3.P.2 Pharmaceutical Development

2. Does the information described in the pharmaceutical development section support the proposed product design, commercial formulation, dosage form, compatibility, specification, and overall control strategy of the drug product?

Applicant's Response:

P.2.1.1 Drug substance

See drug substance reviews for further discussion. Stability data in section P.8 demonstrates that ciprofloxacin is compatible with other components of OTO-201 drug product.

- Solid State Form

Ciprofloxacin drug substance is anhydrous free base form of ciprofloxacin.

(b) (4)

(Amendment dated on May 28, 2015).

(b) (4)

P.2.1.2 Excipients

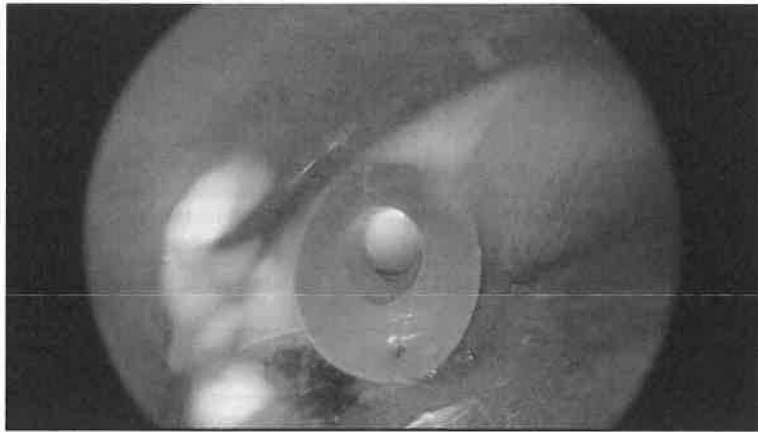
- **Poloxamer 407**

Poloxamer 407 provides gel forming properties to the proposed drug product OTO-201 formulation. The drug product remains a homogeneous suspension around ambient temperature and transition to a gel in situ upon injection into the

body. Figure 1 suggests the relationship between the concentration of poloxamer 407 content and the solution-to-gel formulation. As the drug product is proposed to be delivered at room temperature, (b) (4) TGel is preferred. Initially (b) (4)% of Poloxamer 407 was evaluated; later in vivo PK profile in Guinea pigs suggested (b) (4)% of poloxamer 407 is more optimal for intratympanic applications. Ultimately, (b) (4)% w/w poloxamer 407 diluent formulation with TGel of approximately (b) (4) is reasonable for its intended purpose.



However, the kinetics of gelation is not available in the NDA leaving a paucity in our understanding of the product. We also expressed our concern to the clinical division and Tom Smith stated that this is not critical from a clinical perspective, since clinical trial data demonstrated efficacy in the email communication dated on Oct 6, 2015. In the Amendment dated on Oct 20, 2015, the applicant provided the gelation kinetic study and demonstrated that it takes approximately (b) (4) minutes to reach maximum viscosity reading of the drug product. The detailed method is referred to Section P.4 "Control of Excipients". The picture below illustrates how the material appears after administration into the ear.



- **Tromethamine**

Tromethamine (b) (4) % w/w (b) (4) in the OTO-201 drug product formulation. Hydrochloric acid is used (b) (4)

- **Sodium Chloride**

Sodium chloride (b) (4) % w/w is used to (b) (4) OTO-201 drug product to be consistent with the natural environment of the ear.

P.2.2 Formulation development

Suspensions containing 2% and 6% ciprofloxacin were used in nonclinical studies and in the Phase 1b clinical trial. A 6% ciprofloxacin suspension in (b) (4) poloxamer (b) (4) was selected for further development based on the initial clinical trial. There were no changes in the formulation of OTO-201 drug product (6% ciprofloxacin) throughout clinical development. The formulation provide in table in Question 16 in this review is used in Phase 1, 3 and commercial market.

There is no overage of the drug substance in the formulation.

Details on the temperature cycling stability studies are provided in Section P.2 of the NDA. Attributes including appearance, assay, impurity, temperature of gelation, pH, osmolality, (b) (4) content and particle size distribution were monitored in the study. Results indicate that there was no change in the quality of the product when cycled between (b) (4) refrigerated conditions. Cycling to higher temperatures (b) (4) (b) (4) resulted in a slight increase in (b) (4) levels in the product, all other parameters remained unchanged.

P.2.4 Container Closure System

The primary container-closure system used for ciprofloxacin is summarized in the Table 1.

Table 1: Container-Closure for OTO-201 Drug Product

Component	Component Description	Representative Supplier	DMF Reference
Vial	13mm, 2mL USP type I clear (b) (4) glass vial	[REDACTED]	(b) (4)
Stopper	(b) (4) stopper		
Seal	(b) (4) 13mm aluminum seal with plastic flip-off top		

Prior to filling 2 mL glass vials are [REDACTED] (b) (4)

[REDACTED] The same container closure system was used throughout the drug development. All the vial dimensions remained the same except the height of vial, which was changed [REDACTED] (b) (4).

- Fill Volume Study**

Each vial contains 1 mL of ciprofloxacin suspension for single patient use. The applicant performed a fill volume justification study to confirm the adequacy of the vial fill for one patient. Detailed study was provided in the development report PDR-14-002-01. The test procedure is similar to the dose preparation in the PI. As shown in Tables 2 and 3, 5 patients were able to prepare only two syringes containing of ciprofloxacin suspension out of a single vial. The remaining amount was not sufficient for a third dose.

Table 2: Vial Reconciliation for Bilateral 0.3 mL Withdrawal Volumes

Participant #	Mean (mL) Syringe 1	Mean (mL) Syringe 2	Residual (mL) Remaining	Sum (mL)	% Reconciled
1	0.415	0.403	[REDACTED]	[REDACTED]	(b) (4)
2	0.363	0.327			
3	0.402	0.384			
4	0.397	0.400			
5	0.403	0.364			
Mean (n=15)			0.314	1.086	
SD (n=15)			0.031	0.021	

Table 3: Summary of Accountability for Bilateral 0.3 ml Withdrawal Volumes

Step	Actual Volume Withdrawn (mL)	Reconciled Usage (mL)	Comments
Syringe 1: 18G needle	0.4	0.1	Volume of 18G needle
Syringe 1 priming loss		0.1	Priming to remove bubbles from 20G needle
Syringe 1: 20G suction needle		0.1	Volume of 20G suction needle
Syringe 1 Injection		0.1	Delivered manually from the 0.1 mL mark
Syringe 2: 18G needle	0.4	0.1	Volume of 18G needle
Syringe 2 priming loss		0.1	Priming to remove bubbles from 20G needle
Syringe 2: 20G suction needle		0.1	Volume of 20G suction needle
Syringe 2 Injection		0.1	Delivered manually from the 0.1 mL mark
Residual in vial	0.3	0.3	Only 0.1 mL is retrievable due to vial coating and air bubbles at time of preparation

- Extractable Study**

The applicant performed an extractable study on the primary container closure system. The detailed study including analytical methods and the results is provided in the study report SGS-EL-07-Otonomy-14-002-R.



(b) (4)

Therefore, based on the data provided, no leachable materials were detected above the identification threshold (b) (4) ppm.

- **Container Closure Integrity Study**

The applicant performed Helium Leak test to evaluate container closure integrity on ICH registration batch W0007280. Study report PDR-14-003-01 is provided in the NDA submission. The helium leak rates (b) (4) (b) (4) are within the published leak limit 6×10^{-6} std*cc/sec. Refer to Quality Micro's review for further discussion.

- **Secondary Container Closure System**

Each vial is individually packaged into a minimum (b) (4) carton. Ciprofloxacin suspension is light sensitive, but photostability studies in Section P.8 showed no significant change in the tested quality attributes when the vials of ciprofloxacin are stored inside the (b) (4) cartons. Therefore, the marketing package ((b) (4) carton) appears to provide adequate protection for the proposed drug product from potential photo-degradation.

P.2.5 Microbiological Attributes

Ciprofloxacin suspension is a sterile, preservative free, single patient use suspension packaged in a standard 2 mL Type I glass vial. Ciprofloxacin suspension is tested for sterility and endotoxin at release and on stability.

Refer to Quality Micro's review for detailed discussion.

P.2.6 Compatibility

The applicant performed an in-use compatibility study of ciprofloxacin suspension with the dosing components (syringes and needles) as shown in Table 1.

Table 1: Materials

Material	Manufacturer / Part No.	Intended Use/Function
1 mL Luer Lock Syringe	(b) (4)	Mixing, loading and injection
18 Gauge (b) (4) Needle	(b) (4)	Mixing of drug product and withdrawal from the vial
20 Gauge, 3" (b) (4) (b) (4) Needle	(b) (4)	Injection
6% OTO-201 Drug Product	(b) (4)	Drug product

Table 2 below shows there is little variability between the first and second syringe preparations within and between the participants. All delivered dose are within 90-110% of the intended dose.

Table 2: Dose Uniformity Potency Results for OTO-201 Syringes

Participant No. - Vial No.	Syringe 1	Syringe 2		
1-1	(b) (4)	(b) (4)		
1-2				
1-3				
Participant 1 (n=6); (SD)				
2-1				
2-2				
2-3				
Participant 2 (n=6); (SD)				
3-1				
3-2				
3-3				
Participant 3 (n=6); (SD)				
Overall Mean (n=18); (SD)			107% (0.01)	

(b) (4)

As amended on Apr 24, 2015, study report PDR-14-007-01 was provided to support the above study summary. Also the applicant submitted a repeated study on the registration batch W0007151 after the samples were stored at 2-8 °C and 25°C/60%RH for 12 months in study report PDR-14-010-01. The studies further confirmed the in-use hold time (b) (4) 3 hours at 2-8 °C.

(b) (4)

Reviewer’s Assessment: There is no polymorphic form identified, and since the proposed drug product is formulated as a suspension, the polymorphic form is not a critical quality attribute and has no potential impact on the drug product performance.

In the Amendment dated on May 28, 2015, the applicant states that the solubility data

(b) (4)

A test of particle size distribution is included in the drug product specification with reasonable acceptance criteria.

The excipients used in the drug product and their function have been identified. Refer to P.4 for review of excipients specifications. Tests of Poloxamer 407 content and TGel are included in the drug product specification. The range of Poloxamer 407 content is found acceptable by Pharm/Tox reviewer Dr. James Wild.

No concerns on the stability of the product after (b) (4) refrigerated conditions.

Fill volume studies demonstrated that only two syringes of ciprofloxacin suspension can be prepared from a single vial. No leachable materials were detected above the identification threshold (b) (4) ppm; also the container closure system passed the integrity helium leak test. The marketing package (b) (4) carton) provides adequate protection for the proposed drug product from photo-degradation.

Also studies conducted supports an in-use hold time of (b) (4) at 2-8 °C. The proposed in-use hold time approach was found acceptable during the pre-NDA CMC meeting of IND 112044 (refer to meeting minutes dated on Nov 03, 2014). Dr. Mark Needles, Clinical Reviewer had no concern as expressed via email (dated on Apr 2, 2015) on the proposed hold time.

2.3.P.4 Control of Excipients

3. Is the quality of all excipients adequately controlled with satisfactory specifications?

Applicant's Response:

Specification

As illustrated in Section P.1, all the excipients are compendial.

In addition to acceptance criteria specified in the USP monograph, a test for temperature of gelation is proposed to be performed for Poloxamer 407 raw material.

Table 2: Additional Quality Control Specifications for Poloxamer 407

Excipient	Test	Method	Limits
Poloxamer 407, USP	Temperature of Gelation (Tgel)	Tgel (M11449)	(b) (4)

Analytical Procedures

(b) (4)



Justification of Specifications

All the excipients are compendial and meet the USP standards. The proposed specification limit (b) (4) for the Tgel of Poloxamer 407 excipient is reasonable based on the 5 batches analysis which were in the range (b) (4)

Reviewer's Assessment: Adequate. All the excipients are compendial and are tested in accordance with USP. No excipients of human or animal origins are used in the proposed drug product. The control of excipients present in the drug product is acceptable. The tests and acceptance criteria ensures that the materials are of suitable quality for use in this pharmaceutical product. The proposed TGel limit and its test method, as discussed above are reasonable.

2.3.P.5 Control of Drug Product

4. Is the drug product specification adequate to assure the identity, strength, quality, purity, and potency, and bioavailability of the drug product so that future commercial production batches are comparable to the pivotal clinical batches for the clinical performance in terms of the safety and efficacy?

Applicant's Response:

As amended on Nov 3, 2015, the proposed specifications for OTO-201 drug product for release and stability testing are provided below.

Table 1: Proposed Specification for OTO-201 Drug Product

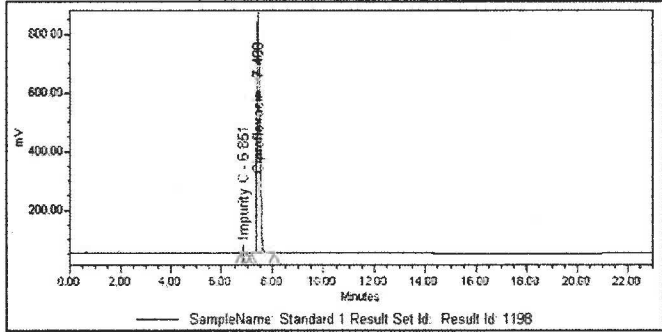
Test	Test Method	Acceptance Criteria
Appearance	M9384 (visual)	White (b) (4), viscous flowing liquid suspension essentially free of visible foreign particulate matter
Identification by HPLC Retention Time	M9388	Conforms
Identification by UV (Photodiode array detector)		Conforms
Assay by HPLC		90.0% to 110.0% of Label Claim
Chromatographic Impurities (b) (4)		NMT (b) (4)% NMT % NMT %
Total Impurities		
Uniformity of Dosage Units (release only)	M9388 (USP <905>)	Conforms
Particle Size Distribution	M9381	NMT (b) (4)
D ₁₀		NMT
D ₅₀		NMT
pH	M9385 (USP <791>)	(b) (4)
Temperature of Gelation	M9387	
Osmolality (5 x diluted sample)	M9386 (USP <785>)	50-70 mOsm/kg
Poloxamer 407 Content (% w/w)	M9383	(b) (4)
Dissolution	M11959	Q = (b) (4) at 60 min
(b) (4)		NMT (b) (4)
(b) (4)		NMT
(b) (4)		NMT
XRPD	M9569	Positive comparison against the OTO-201 reference pattern
Bacterial Endotoxins	MTM-200033 (USP <85>)	NMT (b) (4)
Sterility	MTM-200609 (USP <71>)	Sterile

5. Are all the analytical procedures appropriately described and validated for their intended use?

Applicant's Response:

- *HPLC method for identity, assay, impurities and content uniformity: M9388*

The HPLC method used for determination of identity, assay, impurities and content uniformity of OTO-201 drug product is adequately described in the submission. A summary of the method is shown below.

Column	Zorbax Eclipse Plus C18, 3.5 μ m, 3.0 mm $\times$ 100 mm																					
Mobile Phase	Phase A: 0.1% Phosphate/0.005% Acetone Phase B: 100% Acetonitrile																					
Flow Rate (mL/min)	0.7																					
Injection volume (μL)	10																					
Column Temperature ($^{\circ}$C)	30																					
Detector wavelength (nm)	278																					
Approximate Run Time (min)	23																					
Gradient	<table border="1"> <thead> <tr> <th>Time (Minutes)</th> <th>% Mobile Phase A</th> <th>% Mobile Phase B</th> </tr> </thead> <tbody> <tr> <td>0.0</td> <td></td> <td>(b) (4)</td> </tr> <tr> <td>3.0</td> <td></td> <td></td> </tr> <tr> <td>15.0</td> <td></td> <td></td> </tr> <tr> <td>18.0</td> <td></td> <td></td> </tr> <tr> <td>18.1</td> <td></td> <td></td> </tr> <tr> <td>23.0</td> <td></td> <td></td> </tr> </tbody> </table>	Time (Minutes)	% Mobile Phase A	% Mobile Phase B	0.0		(b) (4)	3.0			15.0			18.0			18.1			23.0		
Time (Minutes)	% Mobile Phase A	% Mobile Phase B																				
0.0		(b) (4)																				
3.0																						
15.0																						
18.0																						
18.1																						
23.0																						
System suitability	Sensitivity (signal-to-noise ratio of positive control) $\leq$ 3; Capacity factor (k): $6 \geq k \geq 2.5$; Resolution $\leq$ 2; Tailing Factor (T) $\geq$ 2; Column Efficiency (N) $\leq$ 5000; n =5, RSD% $\geq$ 2; Standard accuracy: 98.0-102.0%; Overall precision, RSD% $\geq$ 2.																					
Standard chromatogram																						

The HPLC method for assay, ID, impurity and content uniformity for the drug product was successfully validated against established criteria. The method is robust and validated for its intended use. Method validation included specificity, linearity, accuracy, precision, robustness, detection limit and quantitation limit, and stability of solutions.

Attributes	Validation results		
Range	0.05% to 130% of the nominal method concentration, 0.12 mg/mL		
Linearity (Correlation coefficient ≥ 0.999)	Correlation Coefficient: 1.00; y-Intercept: 8480.43; Slope: 52,344,777.47; Residual Sum of Squares: 9,263,902,053.		
Specificity: (Forced Degradation Target: (b) (4)% degradation)	Light 3x ICH defined exposure: average 8.5%; Heat, 70°C, 24hr: average 2.7%; Neutral Hydrolysis, pH 6-8, 70°C, 24hr: average 1.2%; Acid Hydrolysis, 1.0N HCl, 70°C, 24hr: average 1.3%; Base Hydrolysis, 0.5N NaOH, 70°C, 24hr: average 2.6%; Oxidation, 3% H ₂ O ₂ , Ambient, 72hr: average 0.4%.		
Accuracy by Recovery (ciprofloxacin) (Acceptance criteria: Mean percent recovery: 98.0% to 102.0% for each level)	Level (%)	% Recovery (Mean of 3)	%RSD
	70	101.7	0
	100	100.7	0
	130	99.5	0
	Level (%)	% Recovery (Mean of 3)	%RSD
	(b) (4)	104.5	2
Accuracy by Recovery (impurity level) (Acceptance criteria: Mean percent recovery: 80.0% to 120.0% for each level and %RSD (b) (4) for the impurity level)		103.7	1
		102.5	1
		102	1
		101.9	0
Repeatability - Assay [Acceptance criteria: %RSD (n=6) ≤ 2.0]	n=6, mean assay% = 98.4%, RSD% = 0.3%.		
Intermediate Precision - Assay [Acceptance criteria: %RSD (n=6) ≤ 2 for Analyst 2 (n=6) and ≤ 3 for Analyst 1 and Analyst 2 combined (n=12)]	n=6, mean assay% Analyst 2 = 99.8%, RSD% = 0.9%; n=12, mean assay% Analyst 1 and 2 = 99.1%, RSD% = 1.0%.		
Detection Limit (0.005% nominal concentration) (acceptance criteria: Signal to noise ratio ≥ 3 for each of the three injections)	4 to 7		
Quantitation Limit (0.05% nominal concentration) (acceptance criteria: Signal to noise ratio for each injection ≥ 10, %RSD (n=6) for peak area ≤ 30)	50-85; n=6, RSD% = 0.9		
Robustness	stable with variation in mobile phase organic composition ($\pm 10\%$), column temperature ($\pm 2^\circ\text{C}$), and flow rate (± 0.1 mL/minute).		

• **HPLC-SEC method for the quantitation of poloxamer 407: M9383**

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- *Method for particle size distribution: M9381*

Method 9381 on PSD uses the (b) (4) particle size analyzer which utilizes light diffraction of the OTO-201 drug product particles to measure the particle size distribution based on USP <429>. The analytical condition shown below is described in detail in the NDA submission.

Parameter	Setting
Product Refractive Index	(b) (4)
Time Base	
Analysis Time	
Dispersant	
Dispersant Refractive Index	
Sonication Pause	
Sonication Intensity	
Stirrer Rate	
Pump Rate	

The method is adequately validated for its intended use and the validation result is summarized in the table below.

Attributes	Acceptance Criteria	Results
Accuracy	(b) (4)	(b) (4)
Repeatability		
Intermediate Precision		
Robustness		

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Secondary Review Comments and Concurrence: Concur

**Robert H. Wittorf, PharmD.
QAL, OPF/DIA/BRII
10/2/2015**

ASSESSMENT OF THE BIOPHARMACEUTICS INFORMATION

This is a 505 (b)(2) NDA submission for ciprofloxacin, 6% otic suspension to be administered via the intratympanic route of administration. This application is relying on the Agency's prior findings of nonclinical safety for the listed drug product Ciprofloxacin Hydrochloride Tablets (NDA 19537) to incorporate toxicity information for ciprofloxacin administered via the non-otic route. The proposed drug product is indicated for the treatment of middle ear effusion in pediatric subjects with otitis media undergoing tympanostomy tube placement.

The proposed drug product (a.k.a. OTO-201) will be administered intra-operatively as a single, intratympanic dose of 6 mg bilaterally at the time of tympanostomy tube placement.

The Applicant submitted two randomized, prospective, double-blind, sham controlled Phase 3 clinical studies (201-201302 and 201-201303) that enrolled a total of 532 pediatric patients to support the approval of the proposed drug product. The Applicant also submitted a smaller phase 1b trial (201-201101) in support for this NDA.

Review

The Biopharmaceutics review is focused on the evaluation and acceptability of

- 1) the extended release claim
- 2) the dissolution method and acceptance criterion, and
- 3) the information supporting the biowaiver request.

23. Are the in-vitro dissolution test and acceptance criteria adequate for assuring quality control and consistent bioavailability of the drug product?

Yes, the optimized dissolution method (M11959) and the revised acceptance criterion ($Q^{(b)(4)}$ % at 60 minutes) are acceptable.

- a. **What are the highlights of the chemistry and physico-chemical properties of the drug substance (e.g. solubility) and formulation of the drug product?**

Ciprofloxacin is a white (b)(4) powder. Ciprofloxacin is practically insoluble in water, and very slightly soluble in ethanol and methylene chloride. Below is a table showing the solubility profile of ciprofloxacin in various buffers.

Table 1: Ciprofloxacin pH Solubility Profile

Buffer	pH	Solubility (mg/mL)
Citrate	2.6	0.52
Citrate	3.2	0.25
Acetate	4.0	1.66
Citrate	4.1	5.47
Acetate	4.6	6.88
Acetate	4.8	3.08
Acetate	5.3	1.63
Phosphate	6.0	0.12
Phosphate	7.0	0.06
Phosphate	7.9	0.07

The proposed drug product is a sterile, preservative-free otic suspension of 6% (1 mL of 60 mg/mL, w/v ciprofloxacin suspension) ciprofloxacin in a neutral pH buffered, isotonic solution containing a mucoadhesive glycol polymer, poloxamer 407. Upon administration of OTO-201, the formulation gels, thereby enabling the localization and adherence of ciprofloxacin microparticles in the middle ear compartment. The Applicant claims that poloxamer 407 is eliminated from the middle ear, and that the suspended drug particles are slowly solubilized over time resulting in an extended exposure of ciprofloxacin to the middle ear. It is stated in the submission that the sustained exposure of ciprofloxacin is achieved without a controlled release matrix, gel or implant.

Table 2: Formulation of the proposed OTO-201 Drug Product

Ingredient	Quality Standard	Function	% w/w	Composition (mg/mL)
Ciprofloxacin	USP	Active ingredient	(b) (4)	60
Poloxamer 407	NF	(b) (4)	(b) (4)	(b) (4)
Sodium Chloride	USP			
Tromethamine	USP			
Hydrochloric Acid	NF			
Water for Injection (WFI)	USP			
Total				
(b) (4)				

- b. Is there any information on the BCS classification? What claim did the Applicant make based on BCS classification? What data are available to support this claim?**

NA

(b) (4)





(b) (4)

d. What is the proposed dissolution method?

The originally proposed dissolution method is:

USP Apparatus/Sample Cell Size	Flow rate	Medium	Temperature	Medium Volume

(b) (4)



The optimized revised dissolution method is:

USP Apparatus/Sample Cell Size	Flow rate	Medium	Temperature	Medium Volume
USP IV/ (b) (4)	6 min/mL	50 mM Acetate Buffer, pH 4.5	37°C ± 0.5*	480 mL

(b) (4)



Reviewer's Assessment:

The Applicant optimized the dissolution method. Upon subsequent validation, the optimized revised dissolution method is found acceptable.

e. What data are provided to support the adequacy of the proposed dissolution method (e.g. medium, apparatus selection, etc.)?

The Applicant's originally proposed dissolution method had variability issues therefore, the Applicant proposed a newly optimized dissolution method during the review cycle. The dissolution method development is discussed under section f below.

f. What information is available to support the robustness (e.g. linearity, accuracy, etc.) of the dissolution methodology?

The original dissolution method (M9437) was evaluated by the Applicant for system suitability, specificity, range, linearity, accuracy, precision, robustness, and sample and standard solution stability. The original dissolution method was validated for system suitability, specificity, linearity, accuracy, robustness and sample and standard stability. However, for precision, the validation report concluded that (b) (4) failed the pre-determined acceptance criterion for the 6% sample (b) (4)

In order to address the variability issue, the Applicant provided an interim dissolution method development report (052642-0102) on 4/24/2015 in response to FDA's IR letter dated 4/13/2015. In this report, the Applicant investigated (b) (4)

Therefore, the Applicant is proposing to use a new, optimized dissolution method. The Applicant stated that due to the significant changes, the newly optimized method will be validated. However, the Applicant did not provide the validation report for the newly optimized method in a timely manner; therefore, the following IR comment was conveyed to the Applicant on September 18th 2015.

We acknowledge that you have optimized (b) (4) your proposed dissolution method (Seq. 0001 4/27/15). We also noted that the dissolution profiles of the stability samples (Seq. 006 dated 7/24/2015) were generated using the original dissolution method. Therefore, provide:

- *dissolution data demonstrating the discriminating ability of the optimized dissolution method (with respect to critical quality attributes, such as particle size, varying polymer amount etc.),*
- *a method validation report for your newly proposed, optimized dissolution method, and*
- *dissolution data (individual, mean, SD, profiles (b) (4) minutes), and figures) for your registration/stability batches (current time point), and clinical batches and any available fresh drug product batch that you have, using the optimized dissolution method.*

Applicant's Response in an amendment (008) dated 9/23/2015

In response to bullet point #1, the Applicant stated that the newly optimized method is based on the original method and parameters affecting the discriminatory properties remained unchanged.

In response to bullet point #2, the Applicant provided the supplemental validation (i.e. partial validation) on the newly optimized method for system suitability, precision and robustness since the newly optimized method is based on the original dissolution method.

In response to bullet point #3, the Applicant provided the materials-sample information (Table 3) and conditions of the stability samples. In addition, the Applicant provided comparative dissolution data (for the registration/stability batches) obtained using the newly optimized method and the old method. Figure 4 below is an example of comparative dissolution profiles obtained using the newly optimized method (M11959) and the original method (M9437) for batch W0007280 at the 18 month stability time point.

Table 3: Materials-Sample Information

Sample Name	Lot Number	Dose/Strength/ Formulation	Manufacturer	Manufacture Date	Packaging Information
OTO-201 Drug Product	W0007564	6% (60 mg/mL) Ciprofloxacin Suspension	(b) (4)	10-Jun-2014	2 mL Glass Vial
	W0007256			27-Nov-2013	
	W0007280			13-Dec-2013	
	W0007151			28-Sep-2013	
	14239			11-Sep-2014	

Lot Number	Stability Interval (Months)	Condition	(b) (4) Sample ID
W0007564	12	(b) (4)	048134-06-06-0001
			048134-06-06-0002
			048134-06-06-0003
			048134-06-06-0004
W0007256	18	(b) (4)	048134-04-07-0001
			048134-04-07-0002
			048134-04-07-0003
			048134-04-07-0004
W0007280	18	(b) (4)	048134-04-07-0005
			048134-04-07-0006
			048134-04-07-0007
14239	9	(b) (4)	048134-04-07-0008
			057682-01-05-0001
W0007151	24	(b) (4)	057682-01-05-0002
			048134-03-08-0001
			048134-03-08-0002
			048134-03-08-0003
			048134-03-08-0004

Lot Number	Stability Interval (Months)	Condition (b) (4)	PPD Sample ID
14239	12		057682-01-06-0001
			057682-01-06-0002
			057682-01-06-0003
			057682-01-06-0004
W0007564	18		048134-06-07-0001
			048134-06-07-0002
			048134-06-07-0003
			048134-06-07-0004
W0007256	24		048134-04-08-0001
			048134-04-08-0002
			048134-04-08-0003
			048134-04-08-0004
W0007280			048134-04-08-0005
			048134-04-08-0006
			048134-04-08-0007
			048134-04-08-0008

Figure 1: Dissolution Plot for (b) (4) Sample ID 048134-04-07-0007



Reviewer’s Assessment of the Applicant’s Response (S009 dated 9/23/2015):

The Applicant’s statement claiming that the discrimination ability of the newly optimized method is the same as that for the old dissolution method is not acceptable. The discriminating ability is specific for each dissolution method and additionally, the comparative dissolution profiles of the stability batches obtained using the old method and the new method show that dissolution profiles are not similar (as f_2 values were less than 50). Therefore, the Applicant needs to demonstrate the discriminating ability of the newly optimized method.

The following Biopharmaceutics IR Comment was conveyed to the Applicant on September 30th 2015.

In your response to FDA’s IR email dated 9/18/2015, you have stated that parameters affecting the discriminating ability of the optimized dissolution method (M11959)

remained unchanged from the original method (M9437). You have also stated that the changes included in the sample preparation procedure are based on the original method (M9437). However; the comparative dissolution profiles of the stability batches between the old method and the new method show that dissolution profiles are not similar (as indicated by f_2 values less than 50 between the old and the new method for W0007280 at 18 month stability time point). The revised optimized dissolution method is considered a new dissolution method. Therefore, as requested before, we ask that you demonstrate the discriminating ability of the optimized dissolution method and provide a method validation report for your new method (M11959). We acknowledge that you provided dissolution data on your registration/stability batches, however, please provide all the dissolution profiles with standard deviation obtained with the new method in a graphical form to aid in setting dissolution acceptance criteria.

Applicant's Response in an amendment (012) dated 10/15/2015

The Applicant provided the dissolution profiles with standard deviation obtained using the new optimized dissolution method in a graphical form as shown under section 23-j.

Applicant's Response in an amendment (014) dated 10/28/2015

Discriminating ability of the method:

The Applicant's response regarding the discriminating ability of the method is discussed in section 23-g.

Validation of the method:

The Applicant provided a partial validation method report for precision (repeatability and intermediate precision) and robustness of the optimized dissolution method since full validation was performed based on the original dissolution method. The original method was validated for system suitability, specificity, range, linearity, accuracy, sample and standard solution stability. (b) (4)

Therefore, partial validation was performed on the parameters impacted by the differences between the old and the newly optimized method. The system suitability, precision, and robustness (flow rate, sample placement, and glass fill level) were evaluated and validated in the supplemental validation report (the system suitability, repeatability, intermediate precision, and robustness met the acceptance criteria).

Table: Validation Report Summary

Specificity	There is no inference in the dissolution medium blank or placebo
Range	The range of 10% to 125% of the nominal method concentration (0.024 mg/mL) is supported by the linearity, accuracy, and precision data.
Linearity	$r^2 \geq 0.99$.
Accuracy	Acceptance criteria: for the 10% level the accuracy is between 80-120%, for the 25% and 50% level the accuracy is between 90-110%, for the 75%, 100%, and 125% level the accuracy is between 95-105%
Sample and Standard Solution Stability	Sample solutions were shown to be stable for 7 days at ambient conditions and refrigerated conditions

	Initial Precision (%RSD)	Overall Precision (%RSD)	% Standard Comparison
Precision, Flow Rate Robustness	0.0	0.1	99.9
Sample Placement, Media and (b) (4) Robustness	0.0	0.1	100.2
Intermediate Precision	0.1	0.1	100.0
Precision (Repeatability and Intermediate precision)	The absolute difference between the mean results for Analyst 1 and Analyst 2 did not exceed 10% at time points with < 75% dissolved for both analysts and 5% at time points with greater than 75% dissolved for both analysts		

Reviewer's Assessment: ACCEPTABLE

The Applicant has provided sufficient dissolution method development information. The Applicant's validation of the newly optimized method is found acceptable. The precision and robustness (flow rate, sample placement, and glass fill level) of the optimized method were demonstrated. The other parameters such as accuracy, linearity, specificity, solution stability were already validated for the old dissolution method, and remain unchanged.

g. What data are available to support the discriminating power of the method?

The Applicant investigated the discriminating ability of the original dissolution method by varying the particle size (large, target, and small), and amount of poloxamer 407 ((b) (4) %), and the pH of the suspension ((b) (4)) for the original method. However, the discriminating ability for the newly optimized method was requested in an IR dated 9/30/2015 (see section f above).

Applicant's Response in an amendment (014) dated 10/28/2015

Discriminating ability of the optimized dissolution method:

The Applicant varied the particle size ((b) (4)) to evaluate whether the optimized dissolution method can discriminate between these changes.

Dissolution results for batches with different particle sizes (b) (4)

Figure 3-1. Particle Size Variation Dissolution Test



Reviewer's Assessment:

The Applicant failed to provide the particle size distribution (b) (4)

It should be noted that the particle size distribution in the drug product is controlled as part of the drug product specifications (Refer to "Assessment of Process" section in the NDA for detailed discussion).

Change in poloxamer content for drug products with various pHs (b) (4)

3.3. Dissolution Method Discrimination Testing





Reviewer's Assessment:

The optimized dissolution method can discriminate between drug product batches with different polymer content for drug products (b) (4)

[Redacted]

Reviewer's Assessment: ACCEPTABLE

The original method had variability issues. The original method was not discriminating with respect to particle size and unexplained trends were observed when particle size varied (b) (4)

[Redacted]

The Applicant has been requested (IR date 9/30/2015) to provide information regarding the discriminating ability of the newly optimized dissolution method. In their response (amendment (014) dated 10/28/2015), the Applicant provided dissolution data to evaluate the discriminating ability of the method. The provided dissolution data indicate that the optimized dissolution method does not discriminate for change in polymer amount between (b) (4)%. In addition, the optimized dissolution method does not discriminate against the particle size. Therefore, the particle size distribution and the polymer content of the drug product should be controlled (b) (4) drug product specifications.

h. Is the proposed dissolution method bio-relevant? What data are available to support this claim?

N/A

i. What are the proposed dissolution acceptance criteria for this product?

Proposed Acceptance Criteria for Ciprofloxacin
Q = (b) (4)% at 60 minutes

j. What data are available to support the proposed dissolution acceptance criteria?

In amendment 006 dated 7/24/2015, the Applicant provided dissolution data, using the original dissolution method, for five batches that are currently in the stability program. Since the dissolution method was subsequently optimized, the Applicant was requested (IR dated 09/30/2015) to provide dissolution profiles with standard deviation obtained

with the new optimized dissolution method in a graphical form to aid in setting the dissolution acceptance criterion.

Applicant's Response in an amendment 012 dated 10/15/2015

The Applicant provided the dissolution data for samples from the ongoing registration stability program in graphical form along with the summary of the batches tested and timing of the sample on stability generated using the newly optimized dissolution method.

Table 1: Summary of OTO-201 Batches Tested for Dissolution Method Bridging

Batch Number	Batch Designation	Stability Time Point	Storage Condition/ Vial Orientation
W0007256	Registration Batch #2	18 months	(b) (4)
W0007280	Registration Batch #3	18 months	
W0007564	Intended Commercial Process	12 months	
14239	Second Supplier Qualification	9 months	

(b) (4)

The Applicant did not change their proposed dissolution acceptance criterion of $Q = \text{(b) (4)}\%$ at 60 minutes.

Reviewer's Assessment:

The Applicant provided the dissolution data for the registration/stability batches, generated using the newly optimized dissolution method at various stability time points.

(b) (4)

Therefore, it is considered acceptable to set the dissolution acceptance criterion base on dissolution data for batches that are 9 – 18 months old. Based on the provided dissolution profile data for batches that are stored at 5°C (intended storage temperature) for 9-18 months, a dissolution acceptance criterion of $Q = \text{(b) (4)}\%$ at 60 minutes is appropriate.

- k. Is the acceptance criterion acceptable? If not, what is the recommended criterion? Is the setting of the dissolution acceptance criterion based on data from clinical and registration batches? If not, is the setting based on BE or IVIVC data?**

Based on the provided dissolution data using the new optimized dissolution method, the Applicant was requested to revise the dissolution acceptance criterion to $Q^{(b)(4)}\%$ at 60 minutes.

The following Biopharmaceutics IR Comment was conveyed to the Applicant on October 30th 2015.

(b) (4)
Based on the data, a dissolution acceptance criterion of $Q^{(b)(4)}\%$ at 60 minutes should be implemented for the proposed drug product. Revise your drug product specifications and stability protocol accordingly and submit a copy of the updated drug product specifications table.

Applicant's Response dated 11/2/2015 and 11/3/2015

The Applicant updated the specification table with a dissolution acceptance criterion of $Q^{(b)(4)}\%$ at 60 minutes and the newly optimized dissolution method number (M11959).

Reviewer's Assessment: ACCEPTABLE

The Applicant revised the dissolution acceptance criterion to $Q^{(b)(4)}\%$ at 60 minutes.

- l. Are all the strengths evaluated in the pivotal clinical trials? What data are available to support the approval of lower strengths?**

There is only one strength (6%) proposed.

- m. Is there a request for a waiver of the submission of in vivo BE data (Biowaiver)? What is the purpose of the biowaiver request?**

The Applicant requested a waiver of in vivo bioavailability studies with reference to 21 CFR 320.21 (a). The Applicant stated that the proposed product is intended for single administration in each ear via intra-tympanic administration. The Applicant stated the following basis for the biowaiver request:

- 1) There is a large amount of safety and pharmacokinetic information already available for otic administration of ciprofloxacin to pediatric patients.
 - a. Safety: Ciprodex Prescribing Information (Original FDA approval; 19 July 2003); CE Prescribing Information (Original FDA Approval: 01 May 2009).
 - b. Pharmacokinetic: Ciprodex Otic Prescribing Information; data included are peak plasma concentration.
- 2) In nonclinical studies, otic (i.e., the target middle ear compartment) and systemic exposure resulting from a single intratympanic administration of OTO-201 is

comparable to that of a recommended treatment regimen (BID for 7 days) of Ciprodex and Cetraxal.

- 3) From the literature, it is known that ciprofloxacin plasma C_{max} after oral administration of 250 mg is approximately 570-fold higher than the C_{max} after otic administration of Ciprodex 0.84 mg, since:
 - i. A single oral administration of 250 mg ciprofloxacin in adults results in a mean plasma C_{max} of 760 ng/mL
 - ii. A single otic administration of Ciprodex (0.84 mg ciprofloxacin) results in a mean plasma C_{max} of 1.33 ng/mL.
- 4) The total ciprofloxacin delivered dose from OTO-201 is comparable to the total ciprofloxacin delivered dose from Ciprodex:

The recommended treatment regimen of Ciprodex is 0.42 mg ciprofloxacin to each ear twice a day for seven days (6 mg total delivered dose per ear for a total of 12 mg delivered dose) per the Ciprodex Prescribing Information.

The recommended treatment regimen of OTO-201 is 6 mg ciprofloxacin to each ear once following the myringotomy (for a total of 12 mg delivered dose).

The Applicant provided literature data evaluating oral administration of ciprofloxacin. It is reported that C_{max} ranged from 760 ng/mL to 1590 ng/mL after a single 250 mg oral administration in adults^{1,2} (Tartaglione et al., and Bergan et al.)

Table 4: Comparison of Plasma Pharmacokinetic Parameters After Oral Dosing with Ciprofloxacin in 12 Healthy Volunteers

Dose (mg)	Bergan et al., 1987		Tartaglione et al., 1986	
	C_{max} (µg/mL)	t_{max} (h)	C_{max} (µg/mL)	t_{max} (h)
100	0.73 ± 0.28	1.00 ± 0.26		
250	1.59 ± 0.57	1.25 ± 0.44	0.76 ± 0.22	1.12 ± 0.53
500	2.77 ± 1.26	1.54 ± 0.35	1.60 ± 0.79	1.46 ± 0.58
750			2.54 ± 0.54	1.67 ± 0.65
1000	5.57 ± 1.21	1.75 ± 0.67	3.38 ± 0.56	1.80 ± 0.62

Results were reproduced from (Bergan, et al. 1986) and (Tartaglione, et al. 1986).

C_{max} is the maximal plasma concentration.

t_{max} is the time of peak plasma concentration.

The Applicant also provided literature data for pharmacokinetic parameters following the administration of Ciprodex drops into the middle ears of children with tympanostomy

¹ Tartaglione, Teresa, Anita Raffalovich, Wesley Potnor, Ana Espinel-Ingroff, and Thomas Kerkerling. "Pharmacokinetics and tolerance of ciprofloxacin after sequential increasing oral doses." *Antimicrobial Agents and Chemotherapy* 29, no. 1 (1986): 62-66.

² Bergan, T, S.B. Thorsteinsson, I.M. Kolstad, and S. Johnsen. "Pharmacokinetics of ciprofloxacin after intravenous and increasing oral doses." *European Journal of Microbiology* 5, no. 2 (1986): 187-192.

tubes³ (Spektor, Zorik et al.). According to this study, a single-dose (four drops, equivalent to 0.84 mg of ciprofloxacin) of Ciprodex was administered bilaterally through the tympanostomy tubes immediately following tube placement. The mean maximum plasma concentration was 1.33 ± 0.96 ng/mL.

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Reviewer's Assessment:

The Applicant's request for a waiver of in vivo bioavailability studies is granted based on the following justifications:

1. The proposed drug product is intended for local action therefore systemic blood levels are not representative of the efficacy. The Applicant demonstrated the efficacy of the proposed drug product in two Phase 3 studies (201-201302 and 201-201303) in pediatric patients.
2. Based on the literature data, it is estimated that the ciprofloxacin plasma C_{max} after oral administration of a single dose of 250 mg ciprofloxacin (tablet) is approximately 570-fold higher than the C_{max} after a single otic administration of 0.84 mg Ciprodex (solution). It should be noted that the total ciprofloxacin delivered dose from OTO-201 (ciprodex suspension) is comparable to the total ciprofloxacin delivered dose from ciprodex solution (total of about 12 mg (2x2x7x0.42 mg) delivered dose to both ears when 0.42 mg Ciprodex is administered to each ear twice a day for seven days) and total of 12 mg delivered dose to both ears when 6 mg ciprofloxacin is administered as OTO-201(ciprodex suspension) to each ear one time. These findings indicate that the expected

³ Spektor, Zorik, et al. "Pharmacokinetics of CIPRODEX otic in pediatric and adolescent patients." *International Journal of Pediatric Otorhinolaryngology* 72 (2008): 97-102

systemic exposure after otic administration of the proposed drug product is very low.

24. Are the changes in the formulation, manufacturing process, manufacturing sites during the development appropriately bridged to the commercial product?

Bridging is not needed. The same formulation was used in Phase 1b (Study 201-201101) and Phase 3 clinical trials (Studies 201-201302 and 201-201303). The formulation used in the clinical trials is the same as the to-be-marketed formulation.

**OVERALL ASSESSMENT AND SIGNATURES:
BIOPHARMACEUTICS**

Reviewer's Recommendation and Signature:

From the Biopharmaceutics perspective, NDA 207986 for ciprofloxacin 6% otic suspension is recommended for **APPROVAL**.

Please note that the extended release claim designation for this product is not granted.

Date: 11/3/2015

Banu Sizanli Zolnik, Ph.D.
Biopharmaceutics Reviewer
Division of Biopharmaceutics
Office of New Drug Products
Office of Pharmaceutical Quality

Secondary Review Comments and Concurrence:

I concur with Dr. Banu Sizanli Zolnik's assessment and recommendation.

Date: 11/3/2015

Elsbeth Chikhale, Ph.D.
Biopharmaceutics Lead (Acting)
Division of Biopharmaceutics
Office of New Drug Products
Office of Pharmaceutical Quality

ASSESSMENT OF MICROBIOLOGY

Product Quality Microbiology Assessment

**1. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q)
MODULE 3.2: BODY OF DATA**

P DRUG PRODUCT

P.1 Description of the Composition of the Drug Product

- **Description of drug product** – The drug product is a sterile, preservative-free otic suspension of 6% ciprofloxacin in a neutral pH buffered, isotonic solution containing a mucoadhesive glycol polymer, poloxamer 40 for single patient use. Each vial contains approximately 1 mL of 60 mg/mL ciprofloxacin suspension.
- **Drug product composition** –

Ingredient	Function	Content per mL	Content (%w/w)
Ciprofloxacin USP	API	60	(b) (4)
Poloxamer 407 NF			(b) (4)
Sodium Chloride USP			(b) (4)
Tromethamine USP			(b) (4)
Hydrochloric Acid NF			(b) (4)
WFI USP			(b) (4)

- **Description of container closure system** – The drug product will be packaged in a clear 2 mL Type I glass vial with an (b) (4) stopper and aluminum flip-off seal. Additional information on the product’s container closure system is provided in the table below.

Component	Description	Manufacturer
2mL/13mm vial	Type I clear glass	(b) (4)
13mm stopper	(b) (4)	(b) (4)
13mm seal	White aluminum flip off seal	(b) (4)

Acceptable

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

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Storage temperature: 2-8°C; Route of administration: intratympanic administration only; Container: 1.0 mL of 60 mg/mL (6%) ciprofloxacin in a 2mL single-patient use glass vial.

Acceptable

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature: This NDA submission is recommended for approval on the basis of sterility assurance. All microbiology related issues concerning the drug product have been satisfactorily resolved. The container-closure integrity was adequately validated. The facility is appropriately designed and demonstrates a proper flow of material, product and personnel to reduce the risk of contamination. The bulk bioburden acceptance level and bulk hold times are appropriate. The sterility test method validation was performed appropriately. Sterilization (b) (4) processes are supported by adequate validation data.

Duqeh Palmer, Ph.D.
Microbiologist, OPQ/OPF/DMA
10/6/2015

Secondary Review Comments and Concurrence: Concur

John W. Metcalfe, Ph.D.
Microbiology Secondary Reviewer OPQ/OPF/DMA
10/6/2015

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

25. Is the applicant's claim for categorical exclusion acceptable?
26. Is the applicant's Environmental Assessment adequate for approval of the application?

Applicant's Response: This can be adopted from section 1.12.14.

Reviewer's Assessment: Adequate.

The applicant requests a categorical exclusion from the requirement to prepare an environmental assessment under 21 CFR 25.31(b) on the grounds that the concentration of Ciprofloxacin in the aquatic environment is expected to be less than 1 part per billion.

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL

Reviewer's Assessment and Signature:

Adequate. The claim is reasonable and should be acceptable.

Chunchun Zhang, Ph.D.; Review Chemist; Branch 3; Division of New Drug Product I.
Nov 5, 2015.

Secondary Review Comments and Concurrence:

I concur Nov 5, 2015.

Balajee Shanmugam, Ph. D.; Acting Branch Chief; Branch 3; Division of New Drug Product I.

I. Review of Common Technical Document-Quality (Ctd-Q) Module 1

Labeling & Package Insert

1. Package Insert

(a) "Highlights" Section (21CFR 201.57(a))

OTIPRIO (6% ciprofloxacin (b)(4) otic suspension)

For intratympanic administration

Initial U.S. Approval: 2016

————— DOSAGE FORMS AND STRENGTHS —————

(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name		Adequate
Dosage form, route of administration		Adequate
Controlled drug substance symbol (if applicable)		N/A
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths		Adequate

Conclusion: Adequate.

(b) "Full Prescribing Information" Section

3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms		Adequate
Strengths: in metric system		Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.		Adequate

Conclusion: Adequate. Note that the (b) (4) has been denied. The decision has been communicated to the applicant. A revised label reflecting the change will be submitted by the applicant.



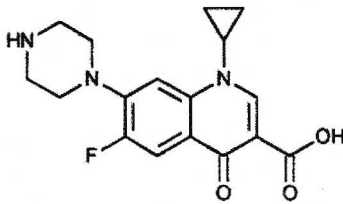
#11: Description (21CFR 201.57(c)(12))

OTIPRIO is supplied as a white, preservative-free, sterile (b) (4) suspension of 6% (w/v) ciprofloxacin in a neutral pH, buffered, isotonic solution in a single-patient use glass vial with a rubber stopper containing 1 (b) (4) mL. (b) (4)

Ciprofloxacin suspension has the following nomenclature:

1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid. Its empirical formula is $C_{17}H_{18}FN_3O_3$ and its molecular weight is 331. (b) (4)

Its chemical structure is as follows:



The inactive ingredients are poloxamer 407, sodium chloride, tromethamine, hydrochloric acid and water for injection (WFI).

The thermosensitive suspension exists as a liquid at room temperature or below and gels when warmed [see *HOW SUPPLIED/STORAGE AND HANDLING (16)*]. (b) (4)

(b) (4)

(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name		Adequate
Dosage form and route of administration		Adequate
Active moiety expression of strength with equivalence statement for salt (if applicable)		N/A
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.		The information is missing in the original NDA submission. Labeling comments are marked up and will be finalized during team labeling review.
Statement of being sterile (if applicable)		Adequate
Pharmacological/ therapeutic class		Adequate
Chemical name, structural formula, molecular weight		The information is missing in the original NDA submission. Labeling comments are marked up and will be finalized during team labeling review.
If radioactive, statement of important nuclear characteristics.		N/A
Other important chemical or physical properties (such as pKa, solubility, or pH)		Adequate

Conclusion: Adequate. Labeling comments are marked up and highlighted in yellow in this review and will be finalized during team labeling review. As indicated above, the claim for extended-release was denied and a revised label will be submitted by the applicant.

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

OTIPRIO is a sterile, preservative-free, (b) (4) otic suspension of 6% (60 mg/mL, w/v) ciprofloxacin in a neutral pH buffered, isotonic solution containing (b) (4) (b) (4) poloxamer 407.

Each **OTIPRIO** carton contains 1 (b) (4) mL of 60 mg/mL (6%) ciprofloxacin in a 2 mL single-patient use glass vial fitted with a rubber stopper. (NDC-69251-201-01)

(b) (4) **OTIPRIO** should be stored 2-8°C until prior to use. Protect from light. (b) (4)

Store in the original carton until dose preparation.

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form		Adequate
Available units (e.g., bottles of 100 tablets)		Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number		Adequate
Special handling (e.g., protect from light, do not freeze)		The information is missing in the original NDA submission. Labeling comments are marked up and will be finalized during team labeling review.
Storage conditions		Adequate

Manufacturer/distributor name listed at the end of PI, following Section #17

Otonomy, Inc.

(b) (4)
San Diego, CA 92121
 (b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)		The information is missing in the original NDA submission. Labeling comments are marked up and will be finalized during team labeling review.

Conclusion: Adequate. Labeling comments are marked up and highlighted in yellow in this review and will be finalized during team labeling review.

2. Container and Carton Labeling

1) Immediate Container Label



(b) (4)

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))		Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))		Adequate
Route of administration (21.CFR 201.100(b)(3))		Not available
Net contents* (21 CFR 201.51(a))		Adequate
Name of all inactive ingredients (Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**		N/A
Lot number per 21 CFR 201.18		Adequate
Expiration date per 21 CFR 201.17		Adequate
“Rx only” statement per 21 CFR 201.100(b)(1)		Adequate
Storage (not required)		N/A
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)		N/A
Bar Code per 21 CFR 201.25(c)(2)***		Adequate
Name of manufacturer/distributor (21 CFR 201.1)		Adequate
Others		N/A

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled “sample”, “physician’s sample”, or a substantially similar statement and the contents of the package do not exceed 8 grams.

**For solid oral dosage forms, CDER policy provides for exclusion of “oral” from the container label

**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Conclusion: Adequate. All the information required to appear on the immediate container label appears on the carton. The claim for extended-release was denied. The applicant will be submitting a revised label to reflect the change.

2) Carton Labeling

(b) (4)

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))		Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100((d)(2))		Adequate
Net contents (21 CFR 201.51(a))		Adequate
Lot number per 21 CFR 201.18		Adequate
Expiration date per 21 CFR 201.17		Adequate
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(d)(2)]		Adequate
Sterility Information (if applicable)		Adequate
“Rx only” statement per 21 CFR 201.100(d)(2), FD&C Act 503(b)(4)		Adequate
Storage Conditions		Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)		Adequate
Bar Code per 21 CFR 201.25(c)(2)**		Adequate
Name of manufacturer/distributor		Adequate
“See package insert for dosage information” (21 CFR 201.55)		The information is missing in the original NDA submission. Labeling

		comments are marked up and will be finalized during team labeling review.
“Keep out of reach of children” (optional for Rx, required for OTC)		N/A
Route of Administration (not required for oral, 21 CFR 201.100(d)(1) and (d)(2))		Adequate

Conclusion: Adequate. Labeling comments are marked up and highlighted in yellow in this review and will be finalized during team labeling review. The claim for extended-release was denied. The applicant will be submitting a revised label to reflect the change.

OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer’s Assessment and Signature:

All product quality labeling comments are marked up and will be finalized during team labeling review.
Chunchun Zhang, Ph.D.; Reviewer Chemist; Branch 3; Division of New Drug Products I.
 Nov 5, 2015

Secondary Review Comments and Concurrence:

I concur Nov 5, 2015.

Balajee Shanmugam, Ph. D.; Acting Branch Chief; Branch 3; Division of New Drug Product I.

II. List of Deficiencies To Be Communicated

All deficiencies have received adequate responses. There are no remaining deficiencies or information requests that need to be conveyed.