CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207986Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA 207986 HFD-520

Trade Name: Otiprio

Generic Name: 6% ciprofloxacin otic suspension

Applicant Name: Otonomy, Inc.

Approval Date, If Known: 12/10/15

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES: X

If yes, what type? Specify: 505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES: X

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

N/A

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

NO: X

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

NO: X

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

NO: X

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

NO: X

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

NO: X

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the

answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 ! !
IND # YES ☐ ! NO ☐
! Explain:

Investigation #2 ! !
IND # YES ☐ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 ! !
YES ☐ ! NO ☐
Explain: ! Explain:

Investigation #2 ! !
YES ☐ ! NO ☐

Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Jane A. Dean, RN, MSN
Title: Regulatory Health Project Manager
Date: 12/10/15

Name of Office/Division Director signing form: Sumathi Nambiar, MD, MPH
Title: Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

JANE A DEAN
12/14/2015

SUMATHI NAMBIAR
12/14/2015

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]		
NDA # 207986	NDA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Otiprio Established/Proper Name: ciprofloxacin 6% Dosage Form: otic suspension		Applicant: Otonomy, Inc. Agent for Applicant (if applicable):
RPM: Jane Dean		Division: Division of Anti-Infective Products

NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) BLA Application Type: ☐ 351(k) ☐ 351(a) Efficacy Supplement: ☐ 351(k) ☐ 351(a)	**For ALL 505(b)(2) applications, two months prior to EVERY action:** • **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.** • **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)** ☒ No changes ☐ New patent/exclusivity *(notify CDER OND IO)* Date of check: ***Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.***

❖ Actions	
• Proposed action • User Fee Goal Date is 12/25/15	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).
[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):
(confirm chemical classification at time of approval)

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other require actions: CST SharePoint)

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Indicate what types (if any) of information were issued	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s)
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☒ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☐ Included
• Original applicant-proposed labeling	☐ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	 7/8/15 6/18/15
❖ Labeling reviews *(indicate dates of reviews)*	RPM: 4/28/15; 8/27/15 DMEPA: 7/23/15; 12/3/15; 12/10/15 DMPP/PLT (DRISK): ☒ None OPDP: 11/18/15 SEALD: ☒ None CSS: ☒ None Product Quality 11/5/15 Other: ☒ None
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	5/18/15 12/7/15
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default htm	
• Applicant is on the AIP	☐ Yes ☒ No

[4] Filing reviews for scientific disciplines are NOT required to be included in the action package.

• This application is on the AIP ○ If yes, Center Director's Exception for Review memo *(indicate date)* ○ If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☐ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC - 1/8/14 If PeRC review not necessary, explain: _____	
❖ Breakthrough Therapy Designation	☒ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*	
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) *(do not include previous action letters, as these are located elsewhere in package)*	X
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	X
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A
• Pre-NDA/BLA meeting *(indicate date of mtg)*	10/2/14
• EOP2 meeting *(indicate date of mtg)*	9/9/13
• Mid-cycle Communication *(indicate date of mtg)*	☒ N/A
• Late-cycle Meeting *(indicate date of mtg)*	☒ N/A
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*	9/19/13 (CMC); 10/24/14 (CMC)
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☐ None
Division Director Summary Review *(indicate date for each review)*	12/10/15
Cross-Discipline Team Leader Review *(indicate date for each review)*	12/10/15
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical	
❖ Clinical Reviews	

• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Clinical review(s) *(indicate date for each review)*	11/20/15
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	Pg. 15
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	X
Clinical Microbiology ☐ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	10/19/15
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Review(s) *(indicate date for each review)*	11/20/15; 11/30/15
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology review(s) *(indicate date for each review)*	10/14/15
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ No separate review
• Supervisory Review(s) *(indicate date for each review)*	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	12/15/11; 12/20/11; 12/5/12; 11/24/15
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested

Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• Tertiary review (*indicate date for each review*)	☒ None
• Secondary review (e.g., Branch Chief) *(indicate date for each review)*	☒ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*	11/5/15
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	11/5/15
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☐ Facilities inspections (*action must be taken prior to the re-evaluation date*) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	☒ Acceptable Re-evaluation date: ☐ Withhold recommendation ☐ Not applicable

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☒ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☒ Done
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☐ Done *(Send email to CDER OND IO)*
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	N/A
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	**N/A**
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☒ Done
❖ Ensure Pediatric Record is accurate	☒ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

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/s/

JANE A DEAN
12/10/2015

From: Dean, Jane
Sent: Tuesday, November 10, 2015 5:52 PM
To: Barbara Finn (BFinn@otonomy.com)
Subject: NDA 207986 (Otiprio) - DMEPA information request

Hi, Barbara - the DMEPA reviewer has the following information request:

Provide a picture of the flap with the etched lot number and expiration date that can be clearly be seen and readable.

This can be sent via email to me. You do not need to make a formal submission to the NDA.

Thanks!

Jane

Jane A. Dean, RN, MSN
Project Manager
DAIP/OAP/OND
Building 22, Room 6397
Office: 301-796-1202
Fax: 301-796-9881
Email: jane.dean@fda.hhs.gov

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/s/

JANE A DEAN
11/10/2015

From: Dean, Jane
Sent: Monday, November 09, 2015 6:20 PM
To: Barbara Finn (BFinn@otonomy.com)
Subject: NDA 207986 (Otiprio) - DMEPA information request re carton and container
Importance: High

Hi, Barbara – the DMEPA reviewer has the following information request related to your email sent earlier today about the placement of the lot number and expiry date:

1. Please provide the rationale on omitting the words “LOT” and “EXP”.
2. Clarify how the end user will interpret the date as expiration date and not production date.
3. Please submit a sample of the proposed carton and the rationale for the changes. (It can be sent directly to me and does not need to be a formal submission).

Jane

Jane A. Dean, RN, MSN
Project Manager
DAIP/OAP/OND
Building 22, Room 6397
Office: 301-796-1202
Fax: 301-796-9881
Email: jane.dean@fda.hhs.gov

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/s/

JANE A DEAN
11/09/2015

From: Dean, Jane
Sent: Friday, November 06, 2015 1:11 PM
To: Barbara Finn (BFinn@otonomy.com)
Subject: NDA 207986 (Otiprio) - carton and container comments from the DMEPA reviewers

Barbara, below are the comments for the carton and containers that the Division of Medication Error Prevention and Analysis (DMEPA) review team has asked me to share with you.

We recommend Otonomy, Inc. submit these revisions below and include labels and labeling that includes approved proprietary name prior to approval of this NDA 207986.

A. Container Label

1. Revise the established name from "[redacted] (b) (4)" to read "ciprofloxacin otic suspension" to be consistent with USP requirements (USP General Chapter <1> Injections, USP General Chapter <1121> Nomenclature) for dosage form.
2. Relocate the strength presentation, "6%", to appear immediately beneath the established name on the main display panel.
3. Revise "[redacted] (b) (4)" statement to read "single- patient use vial – Discard Unused Portion".
4. Remove trailing zero[1], revise the quantity statement "1.0 ml" to read "1 ml" and relocate the quantity statement "1 mL" to appear in the upper right corner of the main display panel for clarity.
5. If space permits, add the route of administration "For Intratympanic Use Only" to appear immediately beneath the strength presentation on the main display panel [see 21 CFR 201.100(b)(3)].

B. Carton labeling

1. See A.1 above

2. See A.2 above

3. See A.3 above

4. Revise the quantity statement from using an error prone trailing zero and to provide important overfill information "[redacted] (b) (4)" to read "1 ml single patient use vial discard unused portion". (Draft Guidance: Container and Carton, April 2013 (lines 469-472).

5. Relocate the route of administration statement, "FOR INTRATYMPANIC USE ONLY", from the side panel to appear on the main display panel immediately beneath the strength presentation on the main display panel [see 21 CFR 201.100(b)(3)] for prominence of important information.

6. Revise the usual dose statement [redacted] (b) (4)" to read "Usual Dosage: 0.1 ml in each affected ear. For Instruction for Use and Preparation: See Prescribing

[1] Guidance for Industry: Guidance for Industry Naming of Drug Products Containing Salt Drug Substances. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM379753.pdf

Information." since safe use of the product is depended on Instruct ion for Use provided in Prescribing Information.

7. For clarity, delete "[redacted] (b) (4)" and revise the storage statement to read "Store at 2^0C to 8^0C (36^0 F to 46^0 F)."

C. Tertiary Container – Twelve-Pack Box

1. See A.1 above

2. See A.2 above

3. See A.7 above

4. Consider revising the last 2 digits of the NDC numbers so that the carton labeling for Tertiary Container – Twelve-Pack Box and carton labeling containing a single vial are different for these two package configurations.

5. Add the statement, "FOR INTRATYMPANIC USE ONLY" to appear on the main display panel immediately beneath the strength presentation, [see 21 CFR 201.100(b)(3)] for prominence of important information.

Jane A. Dean, RN, MSN
Project Manager
DAIP/OAP/OND
Building 22, Room 6397
Office: 301-796-1202
Fax: 301-796-9881
Email: jane.dean@fda.hhs.gov

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/s/

JANE A DEAN
11/06/2015

From: Dean, Jane
Sent: Thursday, November 05, 2015 6:32 PM
To: Barbara Finn (BFinn@otonomy.com)
Subject: NDA 207986 (Otiprio) - statistics information request
Importance: High

Hi, Barbara – the reviewer could not replicate the your Table 11-5 for 'Study treatment failure due to Otorrhea through day 15' in the clinical Study Report of both phase 3 (201-201302 and 201-201303) studies.

The reviewer used the following flags

(b) (4)

Please provide explanations (SAS program with right dataset).

Let me know please what your turn around time will be. Thanks!

Jane

Jane A. Dean, RN, MSN
Project Manager
DAIP/OAP/OND
Building 22, Room 6397
Office: 301-796-1202
Fax: 301-796-9881
Email: jane.dean@fda.hhs.gov

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/s/

JANE A DEAN
11/05/2015

From: Dean, Jane
Sent: Friday, October 30, 2015 5:16 PM
To: Barbara Finn
Cc: Bhandari, Navi
Subject: RE: NDA 207986 OTO-201 General Advice 10/28/2015

Hi, Barbara – I'm forwarding this to you just in case Navi has left for the day. It is the explanation from product quality [redacted] (b) (4):

[redacted] (b) (4)

Jane

From: Bhandari, Navi
Sent: Wednesday, October 28, 2015 5:28 PM
To: Barbara Finn
Cc: Dean, Jane
Subject: RE: NDA 207986 OTO-201 General Advice 10/28/2015

Hi Barbara,

I have asked my team for clarification and will be in touch shortly.

Thank you,

LT Navi Bhandari, Pharm.D, USPHS
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
CDER/FDA
240-402-3815

From: Barbara Finn [mailto:BFinn@otonomy.com]
Sent: Wednesday, October 28, 2015 3:35 PM
To: Bhandari, Navi
Cc: Dean, Jane
Subject: RE: NDA 207986 OTO-201 General Advice 10/28/2015

Hi Navi,

I acknowledge receipt of this message.

May I ask if there is any additional detail surrounding this decision? As you can imagine, this is a topic of interest to us so I want to be clear in my explanation to the team. I point out the attached table from SN

0001, (b) (4)

Also, is there any way we can discuss this decision?

I appreciate your letting me know now and I would appreciate any additional explanation you could provide.

Thanks,
Barbara

From: Bhandari, Navi [mailto:Navdeep.Bhandari@fda.hhs.gov]
Sent: Wednesday, October 28, 2015 12:13 PM
To: Barbara Finn
Cc: Dean, Jane
Subject: NDA 207986 OTO-201 General Advice 10/28/2015
Importance: High

Hello Barbara,

My team has asked that I relay the following comment to you. Please confirm receipt of this message.

(b) (4)

Thank you,
Navi

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/s/

JANE A DEAN
10/30/2015

From:	Bhandari, Navi
To:	"Barbara Finn"
Cc:	Dean, Jane
Bcc:	Shanmugam, Balajee; Chikhale, Elsbeth G; Zolnik, Banu S; Zhang, Chunchun
Subject:	NDA 207986 OTO-201 General Advice 10/28/2015
Date:	Wednesday, October 28, 2015 3:12:00 PM
Importance:	High

Hello Barbara,

My team has asked that I relay the following comment to you. Please confirm receipt of this message.

(b) (4)

Thank you,
Navi

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/s/

NAVDEEP BHANDARI
10/28/2015

From: Dean, Jane
Sent: Thursday, October 22, 2015 1:31 PM
To: Barbara Finn (BFinn@otonomy.com)
Cc: Bhandari, Navi
Subject: NDA 207986 (Otiprio) - product quality information request - following up on 9/30 IR
Importance: High

Hi, Barbara – I just spoke to one of the product quality reviewers and they asked me to follow up with you on when we can expect a response to two items from the 9/30/15 email from Navi. Those two items are:

1. Demonstrate the discriminating ability of the optimized dissolution method, and
2. Provide a method validation report for your new method (M11959).

Please let us know when this information will be coming in. Thanks!

Jane

Jane A. Dean, RN, MSN
Project Manager
DAIP/OAP/OND
Building 22, Room 6397
Office: 301-796-1202
Fax: 301-796-9881
Email: jane.dean@fda.hhs.gov

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/s/

JANE A DEAN
10/22/2015

From: Dean, Jane
Sent: Wednesday, October 14, 2015 1:08 PM
To: Barbara Finn (BFinn@otonomy.com)
Subject: NDA 207986 (Otiprio) - statistics information request - reference to the label

Hi, Barbara – the statistics reviewer has the following two questions regarding calculations submitted in the label:

1. TABLE 2 "Cumulative Proportion of Treatment Failures Through Day 15 in Phase 3 (b) (4)" (on page 7 and listed below the "14. Clinical Studies" section). Please see a copy of your table below and the highlighted reviewers' calculations in red that differed from your calculations.

Table 1: Cumulative Proportion of Treatment Failures Through Day 15 in Phase 3 Clinical (b) (4)

(b) (4)

2. Second paragraph of "14. Clinical (b) (4)" section (reviewers' calculation in red):

(b) (4)

Please let me know when we can expect a response. Thanks!

Jane A. Dean, RN, MSN
Project Manager

DAIP/OAP/OND
Building 22, Room 6397
Office: 301-796-1202
Fax: 301-796-9881
Email: jane.dean@fda.hhs.gov

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/s/

JANE A DEAN
10/14/2015

From: Dean, Jane
Sent: Tuesday, October 13, 2015 11:02 AM
To: Barbara Finn (BFinn@otonomy.com)
Subject: NDA 207986 (Otiprio) - pharm/tox information request - please provide response by 10/20/15

Hi, Barbara, we have quest from the pharm/tox reviewer:

1. We are in agreement with the proposed acceptance criteria for total [redacted] (b) (4) ppm) and specific individual [redacted] (b) (4) [redacted] in the OTO-201 drug product. However, in order to comply with convention, we would like to propose that the acceptance criteria be rounded to whole numbers to eliminate decimal points in the values such that the rounded acceptance criteria values would become [redacted] (b) (4) ppm total [redacted] (b) (4) [redacted] (b) (4) Is Otonomy in agreement with this approach and the new rounded values for the [redacted] (b) (4) total and individual acceptance criteria? Please submit the updated drug product specification and all relevant parts of the NDA reflecting the revised acceptance limits.

2. We note the drug product exists as a suspension at ambient temperature and transitions to become a gel in situ upon injection into the ears. However, the kinetics of gelation is not available in the NDA leaving a paucity in our understanding of the product. Please submit the kinetic study on the gelation time versus temperature.

Thanks

Jane

Jane A. Dean, RN, MSN
Project Manager
DAIP/OAP/OND
Building 22, Room 6397
Office: 301-796-1202
Fax: 301-796-9881
Email: jane.dean@fda.hhs.gov

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/s/

JANE A DEAN
10/13/2015

From:	Bhandari, Navi
To:	"Barbara Finn"
Bcc:	Zolnik, Banu S; Chikhale, Elsbeth G; Matecka, Dorota M
Subject:	NDA 207986 OTO-201 Information Request 9/30/2015
Date:	Wednesday, September 30, 2015 1:32:00 PM
Importance:	High

Hello Barbara,

My team has asked that I relay the following comments to you.

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 ((b) (4)). 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.

Please provide a response by 10/13/2015.

Thank you,
Navi

From: Bhandari, Navi
To: "Barbara Finn"
Bcc: Dean, Jane; Chikhale, Elsbeth G; Zolnik, Banu S
Subject: NDA 207986 OTO-201 Information Request
Date: Friday, September 18, 2015 10:53:00 AM
Importance: High

Good Morning Barbara,

Please see the information request from by team below and provide confirmation of receipt.

Please provide a response by September 23, 2015.

We acknowledge that you have optimized [redacted] (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 [redacted] (b) (4)
- a method validation report for your newly proposed, optimized dissolution method, and
- dissolution data (individual, mean, SD, profiles [redacted] (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.

Thank you,
Navi

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/s/

NAVDEEP BHANDARI
09/18/2015

From: Dean, Jane
Sent: Wednesday, September 16, 2015 1:47 PM
To: Barbara Finn (BFinn@otonomy.com)
Subject: NDA 207986 (Otiprio) - pharmacology/toxicology information request/general advice

Hi, Barbara – the pharmacology/toxicology reviewer has the following observations followed by an information request/general advice:

> [redacted] (b) (4) concentrations in the drug product are of potential concern due to an apparent association with cochlear toxicity in nonclinical studies. In two guinea pig studies (OTO-104-RSP-024 and OTO-104-RSP-025) the [redacted] (b) (4) % poloxamer 407 vehicle with relatively high total [redacted] (b) (4) concentrations (approximately [redacted] (b) (4)) produced cochlear toxicity following intratympanic injections into the round window niche. Given the potential for cochlear toxicity associated with drug product [redacted] (b) (4) content, it is advisable to base the acceptance criteria for total [redacted] (b) (4) in the drug product on concentrations shown to be safe in nonclinical and/or clinical studies.
>
> Based on the results of a guinea pig study (Study No.: OTO-201-RSP-008) where a single intratympanic injection of heat-treated poloxamer 407 did not produce cochlear toxicity, [redacted] (b) (4) concentrations are qualified up to the total [redacted] (b) (4) NOAEL/individual [redacted] (b) (4) NOAELs in this study. Unfortunately [redacted] (b) (4) content was not measured in the batch of [redacted] (b) (4) % poloxamer 407 that was used in Study No. OTO-201-RSP-008 (Batch No.: FG-10-0016), and thus total [redacted] (b) (4) NOAEL/individual [redacted] (b) (4) NOAELs cannot be determined. However, another [redacted] (b) (4) batch of [redacted] (b) (4) % poloxamer 407 (Batch No.: 045-71) was reported to contain [redacted] (b) (4) . Based on the [redacted] (b) (4) content in the 045-71 batch of [redacted] (b) (4) % poloxamer 407, and the results of Study No.: OTO-201-RSP-008, the recommended acceptance criteria for total [redacted] (b) (4) in the OTO-201 drug product is [redacted] (b) (4) .
>
> - Please adjust the acceptance criteria for total [redacted] (b) (4) in the drug product specifications to [redacted] (b) (4) and acceptance criteria for the individual measured [redacted] (b) (4)
>
> - Alternatively, please provide justification for other acceptance criteria for total [redacted] (b) (4) individual [redacted] (b) (4) in the drug product that are qualified by [redacted] (b) (4) NOAEL values in nonclinical studies and/or drug product [redacted] (b) (4) concentrations that have been shown to be safe in clinical studies.

Jane

Jane A. Dean, RN, MSN
Project Manager
DAIP/OAP/OND
Building 22, Room 6397
Office: 301-796-1202
Fax: 301-796-9881

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/s/

JANE A DEAN
09/16/2015

From: Dean, Jane
Sent: Wednesday, September 16, 2015 2:04 PM
To: Barbara Finn (BFinn@otonomy.com)
Subject: NDA 207986 (Otiprio) - product quality microbiology information request

Hi, Barbara - the product quality microbiology reviewer has the following information request:

1. Describe the media used for air, surface and personnel monitoring.

2. State the acceptance criteria/action levels for personnel monitoring.

3. State whether confirmatory spore counts were performed for the (b) (4) (b) (4) used in (b) (4) cycle studies and provide this information.

4. State the number of (b) (4)

5. State the supplier of the (b) (4)

6. Please provide a comparison of the production and media fill rejection criteria.

Please let me know the approximate timeframe for responding. Thank you.

Jane

Jane A. Dean, RN, MSN
Project Manager
DAIP/OAP/OND
Building 22, Room 6397
Office: 301-796-1202
Fax: 301-796-9881
Email: jane.dean@fda.hhs.gov

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/s/

JANE A DEAN
09/16/2015

Pediatric Research Equity Act (PREA) Waiver Request, Deferral Request/Pediatric Plan and Assessment Template(s)

BACKGROUND

Please check all that apply: ☐ **Full Waiver** ☒ **Partial Waiver** ☒ **Pediatric Assessment** ☐ **Deferral/Pediatric Plan**

BLA/NDA#: NDA 207986

PRODUCT PROPRIETARY NAME: Otiprio™

ESTABLISHED/GENERIC NAME: 6% ciprofloxacin (b) (4) **otic suspension**

APPLICANT/SPONSOR: Otonomy, Inc.

PREVIOUSLY APPROVED INDICATION/S:
None

PROPOSED INDICATION:
Treatment of middle ear effusion in pediatric subjects (age 6 months and older) with otitis media undergoing tympanostomy tube placement

BLA/NDA STAMP DATE: February 25, 2015

PDUFA GOAL DATE: December 25, 2015

SUPPLEMENT TYPE:

SUPPLEMENT NUMBER:

Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

NEW ☐ ***active ingredient(s) (includes new combination);*** ☒ ***indication(s);*** ☒ ***dosage form;*** ☒ ***dosing regimen; or*** ☒ ***route of administration?***

Did the sponsor submit an Agreed iPSP? Yes ☒ ***No*** ☐

Did FDA confirm its agreement to the sponsor's Agreed iPSP? Yes ☒ ***No*** ☐

Has the sponsor submitted a Proposed Pediatric Study Request (PPSR) or does the Division believe there is an additional public health benefit to issuing a Written Request for this product, even if the plan is to grant a waiver for this indication? (Please note, Written Requests may include approved and unapproved indications and may apply to the entire moiety, not just this product.)

Yes ☐ ***No*** ☒

Is this application in response to a PREA (Postmarketing Requirement) PMR? Yes ☐ ***No*** ☒

If Yes, PMR # _____ ***NDA #*** _____

Does the division agree that this is a complete response to the PMR? Yes ☐ ***No*** ☐

If Yes, to either question Please complete the Pediatric Assessment Template.

If No, complete all appropriate portions of the template, including the assessment template if the division believes this application constitutes an assessment for any particular age group.

WAIVER REQUEST

Please attach:

☐ ***Draft Labeling (If Waiving for Safety and/or Efficacy) from the sponsor unless the Division plans to change. If changing the sponsor's proposed language, include the appropriate language under Question 4 in this form.***

☐ ***Pediatric Record***

1. Pediatric age group(s) to be waived. A partial waiver for the less than 6 months of age group

2. Reason(s) for waiving pediatric assessment requirements (***Choose one. If there are different reasons for different age groups or indications, please choose the appropriate reason for <u>each</u> age group or indication. This section should reflect the Division's thinking.***)

☒ Studies are impossible or highly impractical (e.g. the number of pediatric patients is so small or is geographically dispersed). (Please note that in the DARRTS record, this reason is captured as "Not Feasible.") If applicable, chose from the adult-related conditions on the next page.

☐ The product would be ineffective and/or unsafe in one or more of the pediatric group(s) for which a waiver is being requested. Note: If this is the reason the studies are being waived, this information MUST be included in the pediatric use section of labeling. Please provide the draft language you intend to include in the label. The language must be included in section 8.4 and describe the safety or efficacy concerns in detail.

☐ The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients **<u>and</u>** is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested.

☐ Reasonable attempts to produce a pediatric formulation for one or more of the pediatric age group(s) for which the waiver is being requested have failed. (Provide documentation from Sponsor) Note: Sponsor must provide data to support this claim for review by the Division, and this data will be publicly posted***. (This reason is for Partial Waivers Only)***

3. *Provide justification for Waiver:*

It is impossible or highly impracticable to include the less than 6 months of age group in clinical studies of pediatric patients with otitis media requiring tympanostomy tube placement. Tympanostomy tube placement is typically not indicated and is rarely performed in this age group. Children less than 6 months of age generally have not manifested the signs and symptoms long enough to diagnose chronic OME. A clinical practice guideline was developed by the American Academy of Otolaryngology—Head and Neck Surgery in 2013 to provide evidence-based indications for the placement of tympanostomy tubes in children. The guidelines recommend offering tympanostomy tube placement to children with bilateral chronic OME lasting at least 3 months with accompanying hearing difficulties.

4. *Provide language Review Division is proposing for Section 8.4 of the label if different from sponsor's proposed language:*

PeRC ASSESSMENT TEMPLATE

Please attach:

- ☐ ***Proposed Labeling from the sponsor unless the Division plans to change. If changing the language, include the appropriate language at the end of this form.***
- ☐ ***Pediatric Record***

Date of PREA PMR:
Description of PREA PMR: ***(Description from the PMC database is acceptable)***

Was Plan Reviewed by PeRC? ☒ **Yes** ☐ **No** If yes, did sponsor follow plan? Yes

If studies were submitted in response to the Written Request (WR), provide the annotated WR in lieu of completing the remainder of the Pediatric Assessment template.

Indication(s) that were studied:

Otiprio for the treatment of pediatric subjects with bilateral middle ear effusion who require tympanostomy tube placement.

Number of Centers

Study 2 (Protocol 201-201302): 29 centers
Study 3 (Protocol 201-201303): 19 centers

Number and Names of Countries __2___

Studies 2 and 3: United States and Canada

Drug information:

- **Route of administration**: Intratympanic (Otic)
- **Formulation:** sterile suspension
- **Dosage:** 6 mg (0.1 ml of 6% ciprofloxacin suspension)

- **Regimen:** A single intratympanic administration into each affected ear during surgery for myringotomy and tympanostomy tube placement

Types of Studies/ Study Design:

Studies 2 and 3 (Protocol 201-201302 and 201-201303): Multi-center, randomized, sham-controlled double blind study to evaluate efficacy and safety of OTO-201 (ciprofloxacin otic suspension 60 mg/ml). A 6 mg dose of OTO-201 was administered as single bilateral intratympanic injections for the treatment of bilateral middle ear effusion in pediatric subjects undergoing tympanostomy tube placement. Sham treatment consisted of single bilateral intratympanic injections of air.

Age group and population in which studies were performed:

Study 2 (Protocol 201-201302): patients aged 6 months to 12 years old
Study 3 (Protocol 201-201303): patients aged 6 months to 11 years old

Number of patients studied or power of study achieved:

Study 2 (Protocol 201-201302): There were 179 patients randomized to the OTO-201 (6% ciprofloxacin suspension) treatment arm and 179 patients who received actual treatment with OTO-201. There were 87 patients randomized to the sham (air) treatment arm and 86 patients who received actual treatment with sham. 60% were male, 61% were less than 2 years, and 83% were less than 4 years.

Study 3 (Protocol 201-201303): There were 178 patients randomized to the OTO-201 (6% ciprofloxacin suspension) treatment arm and 178 patients who received actual treatment with OTO-201. There were 88 patients randomized to the sham (air) treatment arm and 87 patients who received actual treatment with sham. 54% were male, 62% were less than 2 years, and 81% were less than 4 years.

Entry criteria:

Entry criteria for Studies 2 and 3 (Protocols 201-201302 and 201-201303): Pediatric patients ages 6 months to 17 years with a clinical diagnosis of bilateral middle ear effusion requiring tympanostomy tube placement. Only patients with bilateral middle ear effusion on the day of surgery, prior to surgery, were randomized.

Pertinent exclusion criteria for Studies 2 and 3(Protocols 201-201302 and 201-201303):
Patients with a history of prior ear or mastoid surgery, sensorineural hearing loss, or known immunodeficiency

Use of a topical nonsteroidal otic agent within 1 day of randomization Use of a topical/otic corticosteroid within 3 days of randomization or a systemic corticosteroid within 7 days of randomization Use of amoxicillin, Augmentin®, Omnicef®, ceftriaxone, or cephalexin within 3 days of randomization or a fluoroquinolone within 7 days of randomization
Clinical endpoints: Studies 2 and 3 (Protocol 201-201302 and 201-201303): Clinical outcome (assessment for study treatment failure) was the primary endpoint and included the determination of the cumulative proportion of study treatment failures through the Day 15 Visit. A study treatment failure was defined as the occurrence of any of the following events: use of an antibiotic (otic or systemic) anytime postsurgery, otorrhea observed by the blinded assessor on or after the Day 4 Visit, missed visits, or lost to follow up. Safety and tolerability were the secondary endpoints and included the frequency of adverse events and findings from otoscopic examinations, tympanometry, audiometry, vital sign measurements, and physical examination.
Statistical information (statistical analyses of the data performed): Studies 2 and 3(Protocol 201-201302 and 201-201303): For the primary efficacy analysis, patients were evaluated according to the treatment group to which they were originally randomized. The cumulative proportion of study treatment failures through the Day 15 Visit between the OTO-201 and sham group were analyzed using the Cochran-Mantel-Haenszel (CMH) test stratified by age stratum (6 months to 2 years and >2years). The CMH test was conducted at the 2-tailed 0.05 alpha level and estimates of the strength of association were provided using the adjusted relative risk and adjusted odds ratio with their 95% confidence interval (CI). In summary, OTO-201 treatment in both Studies 2 and 3 achieved the primary efficacy endpoint with statistical significance ($p<0.001$). For Study 2 and 3 respectively, there was a 45% and 54% reduction in study treatment failure risk between the OTO-201 and sham treatment groups. For the safety analysis, patients were evaluated according to the actual treatment they received. Treatment-emergent adverse events (TEAEs), serious TEAEs, TEAEs leading to withdrawal from study or death were presented using numbers and percentages of subjects. Shift tables were prepared to summarize findings from otoscopic examination, tympanograms, and audiometry results for all patients in the safety analysis set and each age stratum. Scatter plots of shifts in pure tone average for air conduction and bone conduction average for bone conduction were presented. Descriptive statistical methods for vital sign measurements and changes from screening values were also presented.

Timing of assessments: Studies 2 and 3 (Protocols 201-201302, and 201-201303): Screening (Day -14 to 1), Day 1 (study drug administration), Day 4, Day 8, Day 15, and Day 29 (end of study)
Division comments and conclusions (Summary of Safety and Efficacy) OTO-201 was an effective treatment for pediatric patients with bilateral middle ear effusion who require tympanostomy tube placement. The intratympanic administration of OTO-201 for the proposed indication was safe and well-tolerated in the pediatric population.
Provide language Review Division is proposing for the appropriate sections of the label if different from sponsor-proposed language.

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/s/

JANE A DEAN
09/11/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207986 **INFORMATION REQUEST**

Otonomy, Inc.
Attention: Barbara M. Finn, VP Regulatory Affairs and Quality Assurance
6275 Nancy Ridge Drive
Suite 100
San Diego, CA 92121

Dear Ms. Finn:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ciprofloxacin (ciprofloxacin) [redacted] (b) (4) otic suspension.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response by July 24, 2015, in order to continue our evaluation of your NDA.

Drug product

1. Provide any available stability update for drug product OTO-201.

2. Provide a few samples of the drug product in the commercial container closure system, 2 mL glass vial.

3. We acknowledge your response to Question #3 in the 74-Day Letter to include a test for [redacted] (b) (4) content in the drug product specification. Please revise the appropriate sections to reflect this change and submit the revisions to the NDA.

Process

1. We note that there were [redacted] (b) (4) steps involved in the manufacturing of your phase3/ registration batches; however, [redacted] (b) (4) is now suggested for the intended commercial batches. Please explain the purpose of each [redacted] (b) (4) involved and elaborate how these steps impact the critical quality attributes of the concentrated and final ciprofloxacin suspension.

2. Regarding the batch reconciliation for your batches, please provide a calculation for percent yield obtained at [redacted] (b) (4)

3. Please provide the results of in-process tests for your registration and commercial batches.

4. We acknowledge that you have provided the bulk hold time study information with respect to microbiological controls. Please provide the chemistry related hold time information from similar studies. Please also demonstrate compatibility of your bulk solutions with contact materials used in the manufacturing process.

If you have any questions, call Navdeep Bhandari, Regulatory Health Project Manager, at (240) 402 - 3815.

Sincerely,

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, cn=Balajee Shanmugam -S
Date: 2015.07.09 19:53:46 -04'00'

Balajee Shanmugam, Ph.D.
Acting Branch Chief, Branch III
Division of New Drug Product I
Office of New Drug Products
Center for Drug Evaluation and Research Branch

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 207986

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Otonomy, Inc.
6275 Nancy Ridge Drive, Suite 100
San Diego, CA 92121

ATTENTION: Barbara M. Finn
VP Regulatory Affairs and Quality Assurance

Dear Ms. Finn:

Please refer to your New Drug Application (NDA) dated and received, February 25, 2015, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Ciprofloxacin sterile otic suspension, 6 %.

We also refer to your correspondence, dated and received, April 29, 2015, requesting review of your proposed proprietary name, Otiprio.

We have completed our review of the proposed proprietary name, Otiprio and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your April 29, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017, (http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Karen Townsend, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5413. For any other information regarding this application, contact Jane Dean, Regulatory Project Manager in the Office of New Drugs, at (301) 796-1202.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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

/s/

TODD D BRIDGES
07/08/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207986

FILING COMMUNICATION –
FILING REVIEW ISSUES IDENTIFIED

Otonomy, Inc.
Attention: Barbara M. Finn
Vice President Regulatory Affairs and Quality Assurance
6275 Nancy Ridge Drive, Suite 100
San Diego, CA 92121

Dear Ms. Finn:

Please refer to your New Drug Application dated February 25, 2015, received February 25, 2015, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Ciprofloxacin (6% ciprofloxacin [redacted] (b) (4) otic suspension), 60 mg/mL.

We also refer to your amendment dated April 24, 2015.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by November 6, 2015.

During our filing review of your application, we identified the following potential review issues:

CMC Comments:

1. We note that ciprofloxacin [redacted] (b) (4) during the drug product manufacturing process. Provide solubility data [redacted] (b) (4) of ciprofloxacin.

2. We have evaluated your proposal for not including a test for (b) (4) content in the drug product specification. The data presented indicates that (b) (4) content is controlled in the drug product through end of product shelf-life. However, the data are from a limited number of batches. Furthermore, an increasing trend is observed in samples stored under accelerated conditions although it does seem to be within the (b) (4) limit. Therefore, until more manufacturing experience is gained, please include a test for (b) (4) content in the drug product specification and propose a suitable acceptance criterion. As additional commercial scale product manufacturing is gained post-marketing, it may be feasible to request deletion of the test if adequately supported by a sufficient body of data.

3. Your development reports indicate (b) (4)

4. We were not able to find information on the content uniformity of vials during the filling process. Provide study results by testing assay of the filled vials at the beginning, middle and end of run to ensure that content uniformity of filled vials is under proper control.

5. From our preliminary review we were unable to locate adequate in-process controls for your concentrated ciprofloxacin suspension. Please provide justification for not testing assay, particle size distribution, (b) (4)

6. Provide the bulk solution hold time including available study information for each manufacturing step to support the proposed hold times used. Please define the term (b) (4) since it does not define exact time in units and is therefore difficult to consistently control.

7. Please explain how bulk homogeneity was established. Specifically, indicate what sampling strategy was used (b) (4).

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments captured in the blue lettering:

HIGHLIGHTS GENERAL FORMAT

1. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL. White space missing before several major headings: "Product Title, Indications and Usage, Dosage and Administration, Contraindications, Warnings and Precautions, and Drug Interactions".

2. Section headings must be presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")

• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections. Required "Patient Counseling Information" section heading is missing from Highlights.

HIGHLIGHTS DETAILS

Initial U.S. Approval in Highlights

3. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**. Year 2016 incorrect if approved.

Indications and Usage in Highlights

4. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)". Missing the name of the established pharmacologic class. It should read as follows: "(Product) is a fluoroquinolone antibacterial indicated for . . ."

Adverse Reactions in Highlights

5. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**". Delete the bolded title "(b) (4) "preceding the above bolded verbatim statement under the Adverse Reactions heading in the Highlights section.

Patient Counseling Information Statement in Highlights

6. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

<u>If a product **does not** have FDA-approved patient labeling</u>:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

<u>If a product **has** FDA-approved patient labeling</u>:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling"**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide"**

This "Patient Counseling Information" statement in Highlights is missing.

Contents: Table of Contents (TOC)

7. In the TOC, all section headings must be **bolded** and should be in UPPER CASE. Section headings are not bolded.

8. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)]. Subsections are not indented.

9. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "FULL PRESCRIBING INFORMATION: CONTENTS" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the full prescribing information are not listed." Unbold this statement: "*Sections or subsections omitted from the full prescribing information are not listed."

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

10. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers

8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

17 Patient Counseling Information section missing. According to 21 CFR 201.57 (c)(18), Section 17 (PATIENT COUNSELING INFORMATION) is required. See the Patient Counseling Information Section of Labeling guidance: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM368602.pdf on how to develop this section. Please submit a proposed Section 17.

11. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]"* or *"*[*see Warnings and Precautions (5.2)*]". Cross references within FPI are all capitalized. Only first letter should be capitalized. For example, in section 11, [see HOW SUPPLIED/STORAGE AND HANDLING (16)] should read as [see How Supplied/Storage and Handling (16)] and the entire cross-reference and brackets should be italicized.

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

12. The following heading must be **bolded** and appear at the beginning of the FPI: "**FULL PRESCRIBING INFORMATION".** This heading should be in UPPER CASE. Font is only 8; it should be consistent with the font size of the other headings in the FPI.

ADVERSE REACTIONS Section in the FPI

13. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

    "Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

The above statement or appropriate modification was not included.

Additional Comment for Full Prescribing Information section:
We note that you included [redacted] (b) (4) in Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) to Section 2. See the Guidance for Industry. Dosage and Administration Section of Labeling guidance for further information: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075066.pdf

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by May 29, 2015. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Pediatric studies conducted under the terms of section 505B of the Federal Food, Drug, and Cosmetic Act (the Act) may also qualify for pediatric exclusivity under the terms of section 505A of the Act. If you wish to qualify for pediatric exclusivity please consult Division of Anti-Infective Products. Please note that satisfaction of the requirements in section 505B of the Act alone may not qualify you for pediatric exclusivity under 505A of the Act.

We acknowledge receipt of your request for a partial waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

We note that you have submitted pediatric studies with this application for pediatric patients 3 months to 17 years inclusive. Once the review of this application is complete we will notify you whether you have fulfilled the pediatric study requirement for this age group.

If you have any questions, call Jane A. Dean, RN, MSN, Regulatory Health Project Manager, at (301) 796-1202.

Sincerely,

{See appended electronic signature page}

Sumathi Nambiar, MD, MPH
Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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

/s/

SUMATHI NAMBIAR
05/07/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207986 **INFORMATION REQUEST**

Otonomy, Inc.
Attention: Barbara M. Finn, VP Regulatory Affairs and Quality Assurance
6275 Nancy Ridge Drive
Suite 100
San Diego, CA 92121

Dear Ms. Finn:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ciprofloxacin (ciprofloxacin) [redacted] (b) (4) otic suspension.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response by April 24, 2015, in order to continue our evaluation of your NDA.

Drug Product:

1. In order to further evaluate the requested drug product shelf life, provide statistical analysis of the stability data.
2. Labeling section 1.14.1 mentions that Ciprofloxacin suspension should be administered within [redacted] (b) (4) once drawn into the syringe. In the Pre-NDA CMC meeting dated on Oct. 24, 2014, in response to question 8 you agreed to submit in-use stability study (hold-time study). However, we are unable to locate this information in the NDA. Please indicate where in the NDA this information is presented or submit stability data to support the [redacted] (b) (4) hold time and clarify the storage condition.

Biopharmaceutics:

1. We are unable to locate the supportive information for the [redacted] (b) (4) claim of the proposed product. Provide the location of the supportive information.
2. You have stated on page 21 of 27 of the section 3.2.P.5.6. that the method of sample preparation for dissolution studies has not been optimized, and that additional method validation will be performed and that bridging data between the methods will be collected. Furthermore, you have stated that upon the implantation of the optimized method, the specification for the dissolution testing of OTO-201 drug product will be re-evaluated. Provide timelines for the proposed studies.

3. We are unable to locate the dissolution method development report in the submission. In general, the dissolution method development report should include (but not limited to) the following information:
    a. Detailed description of the dissolution test being proposed for the evaluation of your product and the developmental parameters (i.e., selection of the equipment/apparatus, in vitro release media, flow rate, pH, assay, sink conditions, etc.) used to select the proposed dissolution method as the optimal test for your product. The testing conditions used for each test should be clearly specified. The dissolution profile should be complete and cover at least 85% of drug release of the label amount or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached. We recommend use of at least twelve samples per testing variable;
    b. Provide the complete dissolution profile data (individual, mean, SD, profiles) in SAS transport file format for your product. The dissolution data should be reported as the cumulative percentage of drug dissolved with time (the percentage is based on the product's label claim);
    c. A list of all relevant manufacturing variables and material attributes affecting the dissolution of your proposed product; and
4. Data to support the discriminating ability of the selected dissolution method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the target formulation and the variant formulations that are intentionally manufactured with meaningful variations for the most relevant critical manufacturing variables (i.e., ± (b) (4) % change to the specification-ranges of these variables).

Microbiology:

1. Provide a reprocessing statement.

2. Provide the following WFI information:
    a) Identify sampling Sites and frequencies of sampling.
    b) Provide WFI bioburden and bacterial endotoxin alert and action levels.
    c) Describe actions taken when levels are exceeded.

3. Provide a description of periodic or routine monitoring methods used for yeasts, molds and anaerobes since the bulk drug suspension is stored (b) (4).

4. State all hold times (b) (4), of drug product vials during commercial production. Provide validation for any extended holding periods for the bulk Ciprofloxacin suspension and Poloxamer solution.

5. Clarify whether the [redacted] (b) (4)

6. For the equipment [redacted] (b) (4)

(b) (4)

7. For the vial [redacted] (b) (4)

(b) (4)

8. Provide the following additional information for the media fill runs:

a) State the dates for the media fills. Provide additional results from 3 recent media fill runs if they were performed more than 3 years ago.

b) For each media fill run, provide the filling line speeds, fill volumes, and [redacted] (b) (4)

c) Provide the results for the growth promotion testing that was performed for all media fill runs.

d) Describe actions taken when media fills fail.

If you have any questions, call Navdeep Bhandari, Regulatory Health Project Manager, at (240) 402 -3815.

Sincerely,

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, cn=Balajee Shanmugam -S
Date: 2015.04.13 13:14:52 -04'00'

Balajee Shanmugam, Ph.D.
Acting Branch Chief, Branch III
Division of New Drug Product I
Office of New Drug Products
Center for Drug Evaluation and Research Branch

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207986

NDA ACKNOWLEDGMENT

Otonomy, Inc.
Attention: Barbara M. Finn
Vice President Regulatory Affairs and Quality Assurance
6275 Nancy Ridge Drive, Suite 100
San Diego, CA 92121

Dear Ms. Finn:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Ciprofloxacin (6% ciprofloxacin [redacted] (b) (4) otic suspension), 60 mg/mL

Date of Application: February 25, 2015

Date of Receipt: February 25, 2015

Our Reference Number: NDA 207986

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on April 26, 2015, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i) in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Infective Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call Jane A. Dean, RN, MSN, Regulatory Health Project Manager, at (301) 796-1202.

Sincerely,

{See appended electronic signature page}

Frances V. LeSane
Chief, Project Management Staff
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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

/s/

FRANCES V LESANE
02/27/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 110244

MEETING MINUTES

Otonomy Inc.
Attention: Barbara M. Finn, VP, Regulatory Affairs & QA
6275 Nancy Ridge Drive
Suite 100
San Diego, CA 92121

Dear. Ms. Finn:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for OTO-201 (Ciprofloxacin in (b) (4) Poloxamer 407).

We also refer to the meeting between representatives of your firm and the FDA on October 24, 2014. The purpose of the meeting was to discuss the CMC aspects of the development program for OTO-201 (Ciprofloxacin in (b) (4) Poloxamer 407).

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have questions, call me, at 240-402-3815.

Sincerely,

{See appended electronic signature page}

Navi Bhandari, Pharm.D
Regulatory Health Project Manager
Office of Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-NDA
Meeting Date and Time:	October 24, 2014, 9:00 – 10:00 am, EST
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1419 Silver Spring, Maryland 20903
Application Number:	IND 110244
Product Name:	OTO-201 (Ciprofloxacin in (b) (4) Poloxamer 407)
Indication:	Treatment of middle ear effusion in pediatric subjects with otitis media requiring tympanostomy tube placement.
Sponsor/Applicant Name:	Otonomy Inc.
Meeting Chair:	Stephen Miller, Ph.D.
Meeting Recorder:	Navdeep Bhandari, Pharm.D.

FDA ATTENDEES

Stephen Miller, Ph.D.	Acting Branch Chief
Caroline Strasinger, Ph.D.	Chemistry Reviewer
Jessica Cole, Ph.D.	Product Quality Microbiology Reviewer (via phone)
Okpo Eradiri, Ph.D.	Biopharmaceutics Reviewer
Aleksander Winiarski, Pharm.D	DMEPA Reviewer
Navdeep Bhandari, Pharm.D.	Regulatory Health Project Manager

SPONSOR ATTENDEES

Bob Savel	Otonomy Chief of Technical Operations
Carl LeBel	Otonomy Chief Scientific Officer
Barbara Finn	Otonomy VP, Regulatory Affairs and QA
Debbie Stickels	Otonomy Director, Quality Assurance
Anna Stepanenko	Otonomy Director, Technical Operations
Wayne Liaw, PhD	Otonomy Sr. Director, Pharmaceutical Development
Gerard Lawther	Otonomy Project Manager
David Kashiwase, MBA	CMC Regulatory Consultant to Otonomy

1.0 BACKGROUND

An EOP2 meeting was held on September 19, 2013, and a number of agreements were reached with regard to manufacturing and controls for the OTO-201 drug product and plans for marketing.

A Type B meeting briefing package was submitted September 24, 2014, for an October 24, 2014, CMC Meeting for OTO-201 (Ciprofloxacin in Poloxamer 407, (b) (4)). The NDA is scheduled to be submitted at the end of Q1 in 2015.

2.0 DISCUSSION

The objectives of the meeting are to discuss the CMC aspects of the development program for OTO-201 (Ciprofloxacin in Poloxamer 407, (b) (4)%).

The Agency sent preliminary responses on October 21, 2014 to the Sponsor. The Sponsor asked to focus on questions 1 and 2 under rug substance and questions 5,6,10 and the additional comment regarding dosage and description from the previous meeting.

3.0 QUESTIONS

1. The NDA for OTO-201 will be submitted electronically in the Common Technical Document (CTD) format. Appendix A contains the eCTD table of contents for Modules 1, 2, and 3. Because, this meeting is specific to CMC, Modules 4 and 5 were not included here. Also note that a request for a waiver of *in vivo* Bioavailability studies will be included in the NDA.

   a. Does FDA agree to the proposed format for Section 2.3 and Module 3 (Appendix A**)?**

   b. In Section 3.2.P.R.1 of the NDA (Appendix A**), Executed Production Records, Otonomy proposes to include one representative OTO-201 Drug Product batch record. Does FDA agree with this approach?**

   c. Does FDA have any suggestions regarding the format of these sections to enhance reviewer evaluation?

FDA Response:

a: Refer to response c.

b: We agree with the approach.

c: We note that Module 3.2.A.1 Facilities and Equipment is not planned for submission with the NDA. While this is acceptable, the NDA should contain a brief description of the drug product manufacturing facilities and equipment to support (b) (4) *manufacturing process. For more information on information needed to support an* (b) (4) *manufacturing process, refer to the following Guidance "Sterile Drug Products*

Produced by [redacted] (b) (4)

Discussion: There was no specific discussion on this question.

2. The drug substance specifications are based on the Ciprofloxacin USP monograph. At the End-of-Phase 2 meeting (EOP2), FDA stated that the proposed specifications with inclusion of residual solvent testing was reasonable to support the phase 3 program, but recommended inclusion of a test for particle size distribution (PSD). Section 4.2.1 includes Otonomy's strategy on testing and establishing specifications for PSD.

   a. With respect to PSD, does FDA agree at establishing acceptance criteria based on D50 and D90 data are acceptable?

   b. Does the FDA agree that the proposed specification attributes are adequate to support the NDA filing?

FDA Response:

a. Include D10, D50 and D90 information in the NDA. Appropriateness of the acceptance criterion will be determined in the review cycle.

b. The proposed specification appears adequate to support filing. Acceptability of the proposed drug substance specification will be a review issue.

Discussion: There was no specific discussion on this question.

3. For supply risk mitigation, Otonomy is evaluating additional current Good Manufacturing Practice manufacturers of Ciprofloxacin USP. To support equivalence between the compendial drug substance manufacturers as related to manufacturing of the OTO-201 drug product, Otonomy has proposed a system to add an alternate supplier. Section 4.2.1 includes an outline of criteria for a new supplier.

   Does FDA agree with the proposed system to support inclusion of alternate drug substance manufacturers?

FDA Response:

We agree with the proposed system to support inclusion of alternate drug substance manufacturer [redacted] (b) (4) *assuming the data at release and on stability are comparable to the data from the original site. In the future, when additional suppliers are identified, follow current guidance or submit an alternative proposal in the NDA at that time.*

Discussion: There was no specific discussion on this question.

1.1.1. OTO-201 Drug Product

4. At the EOP2, FDA stated that the attributes in the proposed specification with inclusion of (b) (4) were reasonable to support the NDA. Appendix C contains the development report for the (b) (4) procedure and includes test conditions and the acceptance range.

   a. Does the FDA have any comments regarding development of the (b) (4) method?

   b. Does FDA agree that the attributes being monitored in the proposed specifications (Table 4) are adequate to support the NDA filing?

FDA Response:

a. The (b) (4) method information provided is adequate to address the concerns expressed at the EOP2 meeting. The full method, acceptance criterion, and justification for the specification will be a review issue.

b. We do not agree that the specification is adequate at this time. In the NDA please provide the following information:

- *Define the superscript notation in Table 4 for both the sterility and endotoxin specification.*
- *Given the manufacturing process has been modified, we encourage your to continue to test for (b) (4) Provide full justification and supportive data in the NDA submission and the appropriateness to remove the test will be a review issue.*
- *Given the manufacturing process has been modified, we encourage you to continue to evaluate the ciprofloxacin solid state by (b) (4) as part of your release and stability specification. Provide full justification and supportive data in the NDA submission and the appropriateness to remove the test will be a review issue.*
- *Refer to Question 5 for a response regarding the dissolution method.*

Discussion: There was no specific discussion on this question.

5. Section 4.2.5 and Appendix F contains information on the development of the dissolution method, its validation, and data generated at release and during stability testing of the four registration batches. The method uses Apparatus 4 because of the challenges presented by Apparatus I and Apparatus II. The data generated using this method demonstrated variability introduced by the factors discussed in Section 4.2.5, which makes it difficult to interpret and trend dissolution results obtained for any sampling point prior to 60 minutes. While Otonomy agrees that a dissolution method can be useful as a QC method for this drug product, it might not be feasible to eliminate method variability associated with sample preparation and medium preparation. We believe that quality of the OTO-201 drug product as related to release of ciprofloxacin can be adequately controlled by a combination of the following tests: particle size distribution, Poloxamer content, pH (b) (4). Therefore, we propose that dissolution not be considered one of the attributes to test for the OTO-201 drug product.

Is FDA willing to consider excluding dissolution as one of the attributes for QC testing of OTO-201?

FDA Response:

No, we do not agree that dissolution testing should be excluded as one of the batch release tests for your proposed drug product. The variability observed in a QC test is not indicative that the test itself is not necessary for determining the quality of the drug product. If you wish to deem a different test as a surrogate for dissolution, we recommend that you perform experiments to demonstrate a quantitative relationship between the two tests. Dissolution is a critical test for assessing the quality of drug products, including sterile suspensions, and should therefore be retained in your proposed Specifications Table.

The inclusion of the dissolution method development and validation reports within the briefing package is noted. However, please submit the said reports to the IND as well as to the NDA. Any comments that emanate from our review of the dissolution method development report will be communicated to you either before or after the filing of your NDA. In the interim, we recommend that you explore potential modifications to the dissolution method that are likely to reduce the variability you have described in the briefing document.

Discussion: The Sponsor asked if refinements need to be made to the dissolution method to reduce the observed variability. The Agency advised the Sponsor that if significant changes are made to the method, a cross-validation or bridging of data generated with the old and new methods is likely to be needed; the Sponsor agreed. The Agency also told the Sponsor that if insufficient stability data are generated with a new method, we may request a new stability program post-action. In the interim, the Sponsor will investigate various factors and procedures, including sample preparation, to reduce the variability of the current proposed dissolution method. The Sponsor plans to submit the current dissolution method development report as well as the validation report to the IND in the hope that the Agency can review them and provide feedback prior to NDA filing. The Sponsor plans to submit their NDA at the end of March in 2015. FDA advised the Sponsor to submit the dissolution data package to the NDA as well in the event that the method evaluation in the IND is not completed by NDA filing.

6. Otonomy has determined that the [redacted] (b) (4) A detailed comparison and discussion of the process changes is provided in Section 4.2.2.

Does the FDA agree to Otonomy's approach to show equivalence of the OTO-201 Drug Product manufactured by both processes?

FDA Response:

We note that the data provided suggests that some properties are comparable or improved (e.g. total impurities). However, because the process has been intentionally modified, additional data to support filing of an NDA is needed. Such information would include at least one additional drug product batch to show that the process consistently maintains the desired properties of the drug product including that the (b) (4) *ciprofloxacin is maintained. We recommend that this additional drug product batch be placed on stability and any trends noted be compared to the previous three batches.*

From a microbiology perspective, the NDA should contain a copy of the validation studies conducted to support the (b) (4)
The NDA should also contain information on the bioburden control strategy and the bioburden (b) (4)

Discussion: The Sponsor has found that at (b) (4) **the end product is subject to** (b) (4) **over that utilized for clinical batches. The Sponsor also noted that they have made additional commercial scale batches using an alternate supplier. The Sponsor will provide release data and accelerated data for this new batch at the time of the NDA. The Sponsor stated that 2 commercial scale batches were being made. The first batch utilizing the commercial process has 1 month stability data (accelerated and long term) and 6 months of accelerated and long term data is available for the other batch. The Agency informed the Sponsor that shelf life is supported by the data that is presented at filing, and extensions beyond that time would be a review issue. The Sponsor noted they will submit additional stability data during the review cycle if wanted. The FDA told the Sponsor that supportive stability data may be helpful and Sponsor can submit it to further support the NDA; noting review of additional data will be performed as resources allow. The Sponsor asked if submission of such data would extend the clock and the Agency responded that submission of additional stability data should not extend the clock unless the data indicates a problem. The Sponsor will follow up when that information is available. The Sponsor indicated that they have** (b) (4)

Agency stated that the proposed biological indicator is acceptable, provided that the NDA

contain data that demonstrate the routine product bioburden is less (b) (4) resistant than the proposed biological indicator. The Sponsor will submit the validation studies for time and temperature.

7. Twelve months of long term and six months of accelerated stability data for three registration batches produced using th (b) (4) with six months of long term and accelerated stability will be included in the NDA (See Section 4.2.2 for additional information).

   Does the FDA agree that the proposed stability package is adequate to support the NDA filing?

FDA Response:

Refer to the FDA response to 4b. Additionally, the conduct of annual sterility and endotoxin testing on stability is adequate. Table 12 appears to contain an error as the sterility test acceptance criterion is NMT (b) (4). Please revise Table 12 to correct any errors present with the acceptance criteria. The drug product should be demonstrated to be sterile on stability.

Discussion: There was no specific discussion on this question.

8. At the EOP2 meeting, FDA requested details regarding the design of the proposed in-use study. As discussed in Section 3.1, there are two components to the "in-use" study. The first is truly a hold-time study to be able to advise the treating physician how soon after drawing the two syringes should the prepared injection be used. This will involve preparing syringes for dosing and holding at up to (b) (4) at refrigerator and ambient conditions. This work will be done to directly support the Directions for Use in the label (Appendix B). The second "in-use" evaluation is part of the registration stability protocol in Section 4.2.3. This is being performed at each time point during the registration stability program to confirm that the suspension can be (b) (4)

   Does FDA agree that the in-use stability testing of OTO-201 is adequate to support the NDA filing?

FDA Response:

We generally agree with the approach described. Please note, your study conditions should mimic actual intended use of the product (e.g., agitation time, personnel handling time, and all sample prep procedures).

Discussion: There was no specific discussion on this question.

9. At the EOP2 meeting, FDA requested that Otonomy perform a leachable/extractable study on the commercial container-closure system for OTO-201. The report for the leachable/extractable evaluation was submitted to the IND in SN 0037 along with the

results of the container/closure integrity evaluation of the commercial container-closure system. The reports for both (minus the appendices in the leachable/extractable report) are provided in Appendix E.

Does FDA agree that these data are adequate to support the NDA filing?

FDA Response:

The information appears adequate to support NDA filing.

Discussion: There was no specific discussion on this question.

10. At the EOP2 meeting, there was a request to provide justification for the vial fill of (b) (4), and Otonomy stated that "due to high viscosity of the product, a (b) (4) fill volume is necessary to be able to consistently draw up the correct quantity of 0.1 mL into each of the two syringes needed for administration". A summary of the data supporting the (b) (4) fill volume is included in Section 4.2.2. The complete report was submitted in SN0040.

Does the FDA agree that the approach used to support the OTO-201 vial fill is adequate to support the NDA filing?

FDA Response:

The data you have provided to support your (b) (4) fill volume is adequate to support NDA Filing. However, given the complexity of the preparation of your product along with the risks for medication error associated with the overfill proposed, you must perform a comprehensive use-related risk analysis to identify the use-related risks associated with your proposed product. Your use-related risk analysis must include a comprehensive evaluation of all the steps involved in using your product (e.g., based on a task analysis), the errors that users might commit or the tasks they might fail to perform (e.g., use an incorrect gauge needle to withdraw the drug), the potential negative clinical consequences of use errors and task failures, and the risk-mitigation strategies you plan to employ to reduce any moderate or high risks to acceptable levels (e.g., changes in product design, communication/education plan(s), label and labeling interventions, etc.). We need this information to ensure that all potential risks involved in using your product have been considered and adequately mitigated and the residual risks are acceptable (i.e., not easily reduced further and outweighed by the benefits of the product). Based on this comprehensive use-related risk analysis, you will have a better idea of the extent to which simulated use testing is required. The risk analysis will also guide you in the design of a human factors validation study protocol for your product.

To ensure your approach and methodology are acceptable, please submit your use-related risk analysis and validation study protocol for review prior to study implementation for Agency review and comment. Note that we will need 90 days to review and provide comments under the IND.

Guidance on human factors procedures to follow can be found in Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management, available online at:
http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm094460.htm

Note that we have also published three draft guidance documents that while not yet finalized, might also be useful in understanding our current thinking and our approach to human factors and product design.

Applying Human Factors and Usability Engineering to Optimize Medical Device Design (Draft), available at

http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM259760.pdf

Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (Draft), available at

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

Safety Considerations for Product Design to Minimize Medication Errors (Draft), available at
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM331810.pdf

Discussion: The Sponsor explained that the reason for study of the (b) (4) overfill was to see if it was possible to get another dose out of the vial. The Sponsor's studies indicated that it is not possible to do so. The Sponsor indicated that they are having trouble understanding our guidance and that the documents they read are related to complex devices.

The Agency responded that the guidance was originally developed for devices; however, the general principles in the guidance should be applied for device/drug combination products or products that require atypical steps to prepare doses or to administer the drug. The Agency also noted that the Sponsor's product is not typical in terms of preparation and administration. The Agency requested that the Sponsor develop a risk analysis of the product's preparation steps, assessing potential critical errors and providing mitigation strategies at each individual step. The Agency requested a risk assessment and a usability study protocol to validate the preparation steps to minimize the potential for medication errors.

The Sponsor asked how to validate syringe technique. The Agency told the Sponsor that such a study is similar to the vial fill justification, but it should simulate real use

conditions, including packaging, instructions for use, user groups (e.g. Operating Room [OR] pharmacy staff etc.), simulated order for the dose, and setting (e.g. in the OR pharmacy with all typical equipment [carts, needles, etc.]). The study would include an observer who is assessing the preparation steps and notes any errors during product preparation. The study should be designed to include a minimum of 15 test subjects per user group and should tests all the use scenarios for the product (e.g. preparing a single dose out of a vial and preparing two doses out of a single vial).

Examples of risks which could lead to errors include attempts to withdraw large overfills, changing incorrect gauge needles, not priming the needle, etc. The Agency needs data to assess the criticality of each step and identify all the potential risks for errors and mitigation strategies. The Sponsor asked if the Agency wanted examples in terms of high, medium and low risks. The Agency responded that the Sponsor should assess in their risk assessment the criticality of each step, that is what may happen if a given step is not performed correctly and what will prevent the critical errors. The Sponsor asked if this was a review issue. The Agency responded yes. The Sponsor asked if this risk analysis should be put in IND. The Agency responded yes, as soon as possible. The Sponsor asked if they would still need to provide a usability validation protocol if their risk assessment demonstrated that everything is low risk. The Agency confirmed that the Sponsor would still need to provide a protocol. The Sponsor asked if Agency would provide feedback regarding the protocol and timing, specifically if it would push their submission date as long as there was an agreement on the protocol prior to submission. The Agency responded that we will provide feedback on the protocol and that it will not push back their NDA submission date.

The Agency also noted that in use " (b) (4) **data would be needed to support instructions to the administrator to rechill the vial if the formulation thickens significantly. The sponsor noted that changes caused by** (b) (4)

11. Ciprofloxacin is a well-established and widely used antibiotic.

    With respect to the Environmental Assessment requirement, Otonomy will be requesting a categorical exclusion per 21 CFR 25.31(a), since the quantity of ciprofloxacin being used in OTO-201 is not a meaningful increase in the overall use of the active ingredient. Does the FDA agree with this approach for addressing the Environmental Assessment requirement?

    FDA Response:

    At this time it appears the appropriate categorical exclusion for this application is 21 CFR 25.31(b). The exclusion at 21 CFR5.31(a) is not ordinarily used for a new indication. An adequate justification for the claim of categorical exclusion should be provided in Module 1 of the NDA submission, based on the total direct use of

ciprofloxacin in all Otonomy products. See http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm088977.htm for additional information.

Discussion: **There was no specific discussion on this question.**

Deferred Question from PNDA meeting scheduled on 6-OCT-2014:

Otonomy proposes the following as a descriptor, "[redacted] (b) (4) injectable suspension of ciprofloxacin, for intratympanic use".

Does FDA agree with the proposed product description?

FDA Response:

The information provided at this time is not sufficient to determine the [redacted] (b) (4) *designation of the product. You are encouraged in the NDA submission to provide full justification for the desired designation that includes quantitative data demonstrating* [redacted] (b) (4) *Given the uniqueness of the product, this question will be best addressed in the context of the full drug product information available in the NDA submission and will be a multidisciplinary review decision.*

Discussion: **The Sponsor will provide more justification for the** [redacted] (b) (4) **claim in the NDA and agreed that the decision is multidisciplinary given the uniqueness of the product, and the types of supporting information (e.g., animal studies, comparisons to currently-used therapies, etc.).**

4.0 ADDITIONAL DISCUSSION TOPICS AND AGREEMENTS

The Sponsor will provide a process development report with particle size data in the NDA.

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

/s/

STEPHEN MILLER
11/03/2014
For R.Madurawe

From: Dean, Jane
Sent: Thursday, October 02, 2014 4:04 PM
To: Barbara Finn (BFinn@otonomy.com)
Subject: IND 110244 (OTO-201) - preliminary responses to meeting questions

Hi, Barbara, attached are the preliminary responses to the meeting questions in your briefing document. Please be advised that any new information or data not contained in your meeting package and presented in response to these comments will not be considered for official comment at the scheduled meeting. The information may be very briefly presented, but must be provided as a submission to the application subsequent to this meeting to allow an opportunity for appropriate review and comment.

In preparation for our upcoming meeting, please be advised that the official advice and recommendations of this division will be communicated during the formal dialogue of our upcoming meeting. Any conversations before or after the official meeting will not reflect the decisions or agreements of the division and thus will not be reflected in the official meeting minutes. If follow-up or clarification on a particular issue is required, those issues should be discussed during the meeting or can be pursued through the formal meetings process in a subsequent meeting or teleconference.

If you wish to change this meeting to a telecon, please contact your Project Manager. If you wish to cancel this meeting, the following responses will become part of the administrative record. Submit your cancellation by letter to your application and contact your Project Manager.

If you wish to discuss another application, the official meeting process should be followed as outlined in the May 2009 "*Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants".*

3.3. Questions

3.3.1. Overall Organization

1. The NDA for (b) (4) will be submitted electronically in eCTD format. A draft table of contents (TOC), consistent with CTD/eCTD guidance, is included in Appendix B. It provides an outline of Modules 1 and 2 as well as an outline of the CMC package and nonclinical and clinical reports intended to support the NDA in Modules 3 through 5.

   Does FDA agree that the proposed overall organization of the (b) (4) NDA, with particular attention to the Module 1 Regional Information, would support NDA filing?

   FDA Response to Question 1: Yes.

2. As discussed during the Pre-IND interactions, Otonomy intends to file a 505(b)(2) application for (b) (4) in accordance with 21CFR§314.54, with reference to the literature and data available to FDA in the NDAs of prior approved products containing ciprofloxacin. The NDA TOC in Appendix B and the draft labeling in Section 4 provides specific information on the sections of the NDA/labeling that will rely on prior findings

of safety and efficacy for marketed ciprofloxacin products in support of the (b) (4) NDA.

Does FDA agree that the proposed referenced data available to FDA would support an acceptable 505(b)(2) NDA filing for (b) (4)

FDA Response to Question 2: Yes.

3. The background package contains the statistical analysis plans (SAPs) for the integrated summaries of efficacy and safety (See Appendix C and Appendix D, respectively). Because the clinical program is comprised of 3 single-dose studies (Phase 1b 201-201101 and Phase 3 201-201302 and 201-201303), Otonomy proposes to satisfy the requirements for an integrated assessment of efficacy and safety data in Module 2, Section 2.7.3 Integrated Summary of Efficacy and Section 2.7.4 Integrated Summary of Safety, respectively. This is supported by guidance documents (ICH M4 ECTD – Efficacy and corresponding Q&A document, and the FDA Guidance entitled, "Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document") which state that the submission of a separate ISE and/or ISS is not required when the information provided can be incorporated into the CTD summaries and overview. Further, if the volume of programmed tables and additional output is too vast to place in Module 2, these would be placed on Module 5 (specifically, 5.3.5.3.) and linked to the Module 2 summaries. Lastly, the analysis datasets and additional documentation described in Appendix A will be included in Section 5.3.5.3.

   Does FDA agree to the placement of the integrated summaries of efficacy and of safety in Module 2, Section 2.7.3 Integrated Summary of Efficacy and Section 2.7.4 Integrated Summary of Safety, respectively?

   FDA Response to Question 3: There are situations in which sections 2.7.3, Summary of Clinical Efficacy, and 2.7.4, Summary of Clinical Safety, would be sufficiently detailed to serve as the narrative portion of the ISE and ISS, respectively, while still concise enough to meet the suggested size limitations for Module 2. In such situations, the ISE and ISS can be split across Module 2 and Module 5, with the narrative portion located in section 2.7.3 or 2.7.4 and the appendices of tables, figures, and datasets located in section 5.3.5.3.

3.3.2. Clinical Data

4. The SAP for the Summary of Clinical Efficacy (Appendix C) describes the integrated dataset as consisting of the 2 Phase 3 studies, OTO-201-201302 and OTO-201-201303. This integrated dataset will be used to look at the efficacy of (b) (4) for the combined Phase 3 studies overall as well as the results for the different subsets as delineated in the SAP. The results from the Phase 1b study will be discussed in the summary, but the data itself will not be integrated with the Phase 3 studies. The reason for this is that the Phase 1b study was designed as a sequential dose escalation/dose-finding study, and the doses used in this small study were different from that used in the Phase 3 studies. That coupled with the fact that the Phase 1b study had 83 subjects in contrast with the two

Phase 3 studies that have a total of 532 subjects, support the treatment of the Phase 1b separately for the evaluation of (b) (4) efficacy.

Does FDA agree that the integrated dataset created to look at the efficacy of (b) (4) should be comprised of the two Phase 3 studies?

FDA Response to Question 4: The integrated dataset can consist of the two Phase 3 studies with a Study ID flag to indicate whether the observations come from either OTO-201-201302 or OTO-201-201303.Please clarify if the analysis of the integrated dataset for the Summary of Clinical Efficacy will pool observations across Phase 3 studies.

5. Similar to the situation described for the Summary of Clinical Efficacy, the Summary of Clinical Safety (SAP in Appendix D) will also create an integrated dataset from the two Phase 3 studies and will compare and contrast the results from the Phase 1b. There will, however, be overall subject exposure and disposition from all studies as well as complete listings of important subjects, i.e., those with an SAE or who discontinued a study due to an AE from all three studies.

   Does FDA agree that the integrated dataset created to look at the safety of (b) (4) should be comprised of the two Phase 3 studies with additional overall displays that include the Phase 1b study?

   FDA Response to Question 5: Yes.

6. The Data Standardization Plan in Appendix A outlines the datasets and their format and supporting documentation that will be provided in the NDA to support the clinical studies and the integrated clinical summaries. These datasets are being provided by-study in lieu of individual patient listings (CSR Section 16.4 – See Section 5.4) and CRF tabulations (See Section 5.6.2) and will be comprised of raw datasets and analysis files for the individual studies and analysis files for the integrated datasets. The datasets and documentation for the Phase 3 studies and the Integrated Summaries will be provided in CDISC compliant format. The datasets and documentation for the Phase 1b study will be provided in SDS format and the define.pdf documents for the raw and analysis files are provided in Appendix E. Please note that links in the define.pdf documents to the datasets are not "live", but will be in the NDA submission.

   Does FDA agree with the Data Standardization Plan for the submission of clinical datasets and supporting documentation in the (b) (4) NDA?

   FDA Response to Question 6: The data standardization plan appears sufficient. Please provide codes for the creation of the ADAM files from the SDTM files for each study.

7. Narratives and case report forms for subjects that had a serious adverse event in an (b) (4) study will be included in the NDA (Please note that there were no deaths, no subjects who discontinued due to an AE, and there were no SAEs considered related to

study drug administration). The CRFs will be located in Section 5.3.7 of the NDA and the narratives will be provided in the relevant study report.

Does FDA agree to the plan for inclusion of the narratives and CRFs in the NDA?

FDA Response to Question 7: Yes.

8. Section 3.1 includes details on the number of subjects exposed to [redacted] (b) (4) in the clinical program (356 subjects in Phase 3; 40 subjects in Phase 1b for a total of 396 exposures). In addition Section 3.1 notes that the subset of subjects < 4 years of age with full hearing evaluations is a total of 153 subjects in the OTO-201 group and 67 subjects in the sham group. Otonomy believes this is consistent with the exposures agreed to at the EOP2 meeting and that this supports the filing of an NDA for [redacted] (b) (4)

   Does FDA agree that the total number of exposures, including the subset of subjects < 4 years of age with full hearing evaluations is adequate to support the filing of an NDA for [redacted] (b) (4)

   FDA Response to Question 8: Yes.

9. At the End-of-Phase 2 meeting held 09SEP2013, it was agreed that Otonomy would submit a request for a waiver of in vivo bioavailability studies for [redacted] (b) (4) The request for a waiver of in vivo bioavailablity studies for [redacted] (b) (4) was submitted to IND 110244 in SN 0027 on 28JAN2014. Feedback was obtained via email on 03JUL2014. It is understood that a formal response on the waiver will not occur until the NDA is under review. The additional data that will be provided in the waiver submitted with the original NDA is comprised of a nonclinical comparison of ciprofloxacin levels in plasma and at the target tissue (i.e., middle ear), when administered as OTO-201, Cetraxal® Otic drops, or Ciprodex® Otic drops (See Section 3.1.1).

   Does FDA agree that the waiver for *in vivo* clinical bioavailability studies for [redacted] (b) (4) **would be possible with the data described in the background package and that acceptance and approvability of an NDA for** [redacted] (b) (4) **would not be impeded by the absence of in vivo clinical bioavailability data for** [redacted] (b) (4)

   FDA Response to Question 9: The inclusion of the nonclinical exposure data in the NDA to support the biowaiver request will not be a fileability issue. However, a final decision on granting the biowaiver request, and the potential impact on approvability of the NDA, are review issues.

3.3.3. Clinical Microbiology

10. At the Pre-IND meeting held 27SEP2010 for a related drug product, [redacted] (b) (4), the Division recommended that Otonomy provide data on the mechanisms of resistance and the epidemiology of ciprofloxacin resistance. This data should be recent (within the last

three years) and may be obtained from the literature. [N.B., The literature search and report was completed prior to the original IND for OTO-201 and submitted in SN 0003.] In addition, the Division recommended that Otonomy perform time-kill studies with the target concentration of ciprofloxacin against ciprofloxacin-resistant organisms that are potential pathogens in this indication. At the End-of-Phase 2 meeting, Otonomy committed to completing these in parallel with Phase 3 and submitted the results of these evaluations to IND 110244 in SN 0036 on 30JUN2014. Otonomy believes that this requirement is now complete and no additional evaluations of this nature will be required to support the NDA for (b) (4)

Does FDA agree that the requests for Microbiology data related to resistance and time-kill for ciprofloxacin have been fulfilled and no additional evaluations of this nature are needed to support an NDA for (b) (4)

FDA Response to Question 10: We agree that no additional evaluations with respect to the above requests are required at this time.

3.3.4. General

11. (b) (4) will be injected by a trained health care professional in a surgical setting. Because of this, the fact that (b) (4) had an acceptable safety profile in the clinical program, and the fact that ciprofloxacin has been administered via otic drops for more than 10 years to a similarly aged population, routine risk assessment and risk minimization will be accomplished through professional labeling and adverse event monitoring and reporting. Otonomy believes there is no need for a Risk Evaluation and Mitigation Strategy (REMS) for (b) (4)

    Does FDA agree that a REMS is not needed for (b) (4)

    FDA Response to Question 11: We agree that it is not necessary to include a REMS in your NDA submission.

12. (b) (4)

(b) (4)

Does FDA agree with the proposed product description?

FDA Response to Question 12: We defer to the Chemistry, Manufacturing and Controls meeting taking place October 24, 2014, for response to this question.

Jane

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

/s/

JANE A DEAN
10/02/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 110244

MEETING PRELIMINARY COMMENTS

Otonomy, Inc.
Attention: Carl LeBel
Chief Scientific Officer
6275 Nancy Ridge Drive Suite 100
San Diego, CA 92121

Dear Dr. LeBel:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for OTO-201 (Ciprofloxacin in (b)(4)% Poloxamer 407).

We also refer to your July 25, 2013, correspondence, received July 25, 2013, requesting a meeting to discuss proposed CMC development components in order to gain approval of OTO-201. Otonomy also seeks concurrence that the proposed CMC program is adequate to support the NDA filing and ultimate approval of OTO-201 as an intra-operative treatment of middle ear effusion in pediatric subjects requiring tympanostomy tube placement.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have questions, call me, at 240-402-3815.

Sincerely,

{See appended electronic signature page}

Navi Bhandari, Pharm.D
Regulatory Health Project Manager
Office of Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type:	Type B
Meeting Category:	End of Phase 2 CMC Meeting
Meeting Date and Time:	September 19, 2013 10:30 AM to 11:30 PM
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1419 Silver Spring, Maryland 20903
Application Number:	IND 110244
Product Name:	OTO-201 (Ciprofloxacin in (b)(4)% Poloxamer 407).
Indication:	Intra-operative treatment of middle ear effusion in pediatric subjects requiring tympanostomy tube placement.
Sponsor/Applicant Name:	Otonomy

FDA ATTENDEES (tentative)

Office of New Drug Quality Assessment (ONDQA)

Rapti D. Madurawe, Ph.D.	Branch Chief
Dorota M. Matecka, Ph.D.	CMC Lead
Navdeep Bhandari, Pharm.D	Regulatory Health Project Manager
Althea Cuff, MS	Regulatory Health Project Manager
Jane Dean	Regulatory Health Project Manager
James Vidra, Ph.D.	Chemistry Reviewer
Angelica Dorantes, Ph.D.	Biopharmaceutics Team Leader
Kelly Kitchens, Ph.D.	Biopharmaceutics Reviewer

Division of Anti-Infective Products (DAIP)

Brittany Goldberg, MD	Medical Officer
Thomas Smith, MD	Lead Medical Officer
Andres Alarcon	Staff Fellow

New Drug Microbiology Staff

Steven Donald, Ph.D.	Microbiologist

SPONSOR ATTENDEES

Carl LeBel, PhD	Chief Scientific Officer
David Weber, PhD	Chief Executive Officer
Jerry Wroblewski	Chief Operations Officer
Wayne Liaw, PhD	Director of Pharmaceutical Development
Barbara Finn	Regulatory Consultant

(b) (4)

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for September 19, 2013, 10:30 AM to 11:30 PM, FDA White Oak Building 22, Conference Room: 1419 between Otonomy and ONDQA. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting.

1.0 BACKGROUND

Otonomy seeks FDA concurrence on the proposed CMC development components in order to gain approval of OTO-201. Otonomy also seeks concurrence that the proposed CMC program is adequate to support the NDA filing and ultimate approval of OTO-201 as an intra-operative treatment of middle ear effusion in pediatric subjects requiring tympanostomy tube placement.

2.0 QUESTIONS

1. **Does FDA concur that the proposed drug substance specifications that incorporate the Ciprofloxacin USP requirements are adequate to support Phase 3 Studies and a NDA filing?**

   Agency Response:

   The proposed drug substance (DS) specification that incorporates the Ciprofloxacin USP requirements and additional tests such as residual solvents test is considered reasonable to support Phase 3 clinical studies. We recommend inclusion of a test for particle size distribution in the DS specification. Note that the adequacy of the DS specification (tests, analytical procedures and acceptance criteria) will be assessed based on the overall data submitted to the NDA.

2. **Does the FDA concur that the attributes included in the proposed Poloxamer 407 specifications are adequate to support Phase 3 studies and a NDA filing?**

   Agency Response:

The test attributes included in the proposed Poloxamer 407 specification appear reasonable. However, it is up to the NDA applicant to demonstrate that the specifications (particularly the acceptance criteria) for Poloxamer 407 are appropriate for the proposed drug product. Note that the adequacy of the proposed Poloxamer 407 specification (tests, analytical procedures and acceptance criteria) will be assessed based on the overall data submitted to the NDA.

3. **Does the FDA concur that the attributes included in the proposed DP specifications are appropriate to support Phase 3 studies and a NDA filing?**

Agency Response:

The attributes included in the proposed drug product (DP) specification appear reasonable. We recommend inclusion of a test for gelation time in the drug product specification. A detailed description of analytical procedures should be provided in the NDA for each of the tests proposed in the DP specification. In addition, the acceptance criteria proposed for each of the attributes, including (b) (4) levels, will need to be proposed and appropriately justified. Also, see additional comments (below) regarding the dissolution method.

It is stated that the sterility test was performed using a modified USP <71> Test and the Specification Table 10 identifies the sterility test as (b) (4). Please identify the test method, the manufacturer and provide a brief overview of the sterility test protocol. Validation of the sterility test method will be required at the time of the NDA submission.

Note that the adequacy of the proposed DP specification (tests, analytical procedures and acceptance criteria) will be assessed based on the overall data submitted to the NDA.

4. **Does the FDA concur that the proposed stability protocol is adequate to support the NDA filing?**

Agency Response:

The proposed stability protocol appears adequate. We recommend inclusion a test for gelation time in the stability tests. Please also refer to the response to Question 3.

Note that at the time of submission, the NDA should include at least 12 months of long-term and 6 months of accelerated stability data for three registration batches of the drug product packaged in the container closure system proposed for marketing.

5. **Does the FDA concur that the proposed in-use stability evaluations and the frequency of**

testing are adequate to support the NDA filing?

Agency Response:

Your proposal is unclear. Please provide details of the proposed in-use stability study. Tests for resuspension (i.e., adequate particle size distribution and ability to pass through the syringe) should be included in each time interval under the stability protocol.

6. **Does the FDA concur that this vial stability approach is acceptable to support the NDA filing?**

Agency Response:

Although the glass vial stability approach appears reasonable, justify why two vial configurations are proposed for commercialization. In addition, please conduct the leachable/extractable study on the commercial container/closure system by using screening analytical methods (such as HPLC, GC etc.) on at least one stability batch through expiry.

7. **Does the FDA concur with the proposed administration for OTO-201?**

Agency Response:

We acknowledge that the non-preserved drug product vial is labeled as single use and that the unused portion should be discarded. However, we are concerned that excessive fill volumes would result in improper use of a non-preserved product. Please justify the (b) (4) fill volume when only (b) (4) is the required dose.

The proposed administration of OTO-201 drug product appears reasonable from a product quality perspective.

3.0 Additional Comments:

We have the following advice comments for the information that should be provided in your NDA regarding the development of the dissolution method and establishing dissolution acceptance criteria for your product:

1. **Dissolution Testing:** Provide the dissolution method report supporting the selection of the proposed test method. This report should include the following information:

   a. Solubility data for the drug substance covering the pH range;

   b. Detailed description of the dissolution test being proposed for the evaluation of your product and the developmental parameters (i.e., selection of the equipment/apparatus, in-vitro release media, agitation/rotation speed, pH, assay,

sink conditions, etc.) used to select the proposed dissolution method as the optimal test for your product. If a surfactant was used, include the data supporting the selection of the type and amount of surfactant. The testing conditions used for each test should be clearly specified. The dissolution profile should be complete and cover at least 85% of dissolution of the label amount or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached. We recommend the following sampling time points 0.5, 1, 2, 4, 6, 8, and 12 hours, and the use of at least twelve samples per testing variable;

c. Provide the complete dissolution profile data (individual, mean, SD, profiles) for your product. The dissolution data should be reported as the cumulative percentage of drug dissolved with time (the percentage is based on the product's label claim);

d. Data to support the discriminating ability of the selected dissolution method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the reference (target) product and the test products that are intentionally manufactured with meaningful variations for the most relevant critical manufacturing variables (i.e., ± (b) (4) % change to the specification-ranges of these variables).

2. **Dissolution Acceptance Criteria:** Provide the complete dissolution profile data (i.e. 10, 20, and 30 minutes; 1, 2, 4, 6, 8, 10, and 12 hours) from the clinical and stability registration batches supporting the selection of the dissolution acceptance criteria (i.e., specification-sampling time points and specification values). For the setting of the dissolution acceptance criteria, the following points should be considered:

a. The dissolution specifications should encompass the timeframe over which at least 85% of the drug is dissolved or where the plateau of drug dissolved is reached if incomplete dissolution occurs.

b. Data from the lots used in the clinical trials and primary stability studies must be used.

c. For (b) (4) products, the establishment of at least three specification time points covering the initial, middle, and terminal phases of the complete dissolution profile data must be set. The acceptance criteria ranges must be based on the overall dissolution data generated at these times.

d. In general, the selection of the dissolution acceptance criteria ranges is based on mean target value (b) (4) % and NLT (b) (4) % for the last specification time-point. Wider specification ranges may be acceptable if they are supported by an approved *In-Vitro In-Vivo* Correlation (IVIVC) model.

e. The dissolution acceptance criteria should be set in a way to ensure consistent performance from lot to lot and these criteria should not allow the release of any lots with dissolution profiles outside those that were tested clinically.

Note that the final determination on the acceptability of the dissolution method is a review issue that can be determined during the IND or NDA. However, the acceptability of the proposed dissolution acceptance criteria for your product will be made during the NDA review process based on the totality of the provided data.

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/s/

DOROTA M MATECKA
09/17/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 110244

MEETING MINUTES

Otonomy, Inc.
Attention: Carl LeBel, PhD
Chief Scientific Officer
6275 Nancy Ridge Drive
Suite 100
San Diego, CA 92121

Dear Dr. LeBel:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for OTO-201.

We also refer to the meeting between representatives of your firm and the FDA on September 9, 2013. The meeting was an End-of-Phase 2 meeting. The purpose was to obtain the Division's concurrence with the proposed Phase 3 study design and that the proposed nonclinical program was adequate to support NDA filing.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Jane A. Dean, RN, MSN, Regulatory Health Project Manager at (301) 796-1202.

Sincerely,

{See appended electronic signature page}

Sumathi Nambiar, MD, MPH
Acting Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: End-of-Phase 2

Meeting Date and Time: September 9, 2013
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room 1419
Silver Spring, Maryland 20903

Application Number: IND 110244
Product Name: OTO-201
Indication: Intra-operative treatment of middle ear effusion in pediatric subjects requiring tympanostomy tube placement
Sponsor/Applicant Name: Otonomy, Inc.

Meeting Chair: Sumathi Nambiar, MD, MPH
Meeting Recorder: Jane A. Dean, RN, MSN

FDA ATTENDEES
Division of Anti-Infective Products:

Andres Alarcon, MD	Clinical Reviewer
Kimberly Bergman, PharmD	Clinical Pharmacology Team Leader
Jane A. Dean, RN, MSN	Regulatory Health Project Manager
Maureen Dillon Parker	Chief, Project Management Staff
Katherine Laessig, MD	Deputy Director
Sumathi Nambiar, MD, MPH	Acting Director
Wendelyn Schmidt, PhD	Pharmacology/Toxicology Team Leader
Thomas Smith, MD	Clinical Team Leader
Kerry Snow, MS	Acting Clinical Microbiology Team Leader
Thamban Valappil, PhD	Statistics Team Leader
James Wild, PhD	Pharmacology/Toxicology Reviewer

SPONSOR ATTENDEES
Otonomy

(b) (4)

Celine Delpouys	Director, Program Management
Barbara Finn	Regulatory Consultant

(b) (4)

Carl LeBel, PhD	Chief Science Officer
Eric Mair, MD	Pediatric Otolaryngologist
David Weber, PhD	Chief Executive Officer

1.0 BACKGROUND

Otonomy, Inc. requested an End-of-Phase 2 meeting on June 28, 2013. The meeting was scheduled for September 9, 2013. Otonomy submitted a briefing document on August 9, 2013, which contained background information and specific meeting questions. The Division provided preliminary responses to the meeting questions on September 4, 2013, via email which are identified as **FDA Response**. The questions are repeated below **in bold** with the preliminary responses. Comments during the meeting are captured under **Discussion** following each question.

In the Introduction section of the meeting package, Otonomy stated the following: "Otonomy has successfully completed the Phase 1b OTO-201101 study entitled, "A Randomized, Double-Blind, Placebo- and Sham-Controlled, Multicenter, Phase 1b Study of OTO-201 Given as a Single Intratympanic Injection for Intra-Operative Treatment of Middle Ear Effusion in Pediatric Subjects Requiring Tympanostomy Tube Placement." These results support initiating Phase 3 studies for OTO-201 as an intra-operative treatment of middle ear effusion in pediatric subjects requiring tympanostomy tube placement. The background package provides a target product profile, a summary of the nonclinical and clinical information generated to date, the design of the Phase 3 studies, and the intended number of exposures once the clinical program is complete."

2. DISCUSSION

After introductions, the meeting was turned over to Otonomy so they could focus on the Division responses that needed clarification.

1.7.1. Nonclinical

a. Does the FDA concur that the nonclinical development program that has been conducted by Otonomy adequately supports the NDA filing for OTO-201 in pediatric subjects with middle ear effusion requiring tympanostomy tube surgery placement?

FDA Response: The scope of nonclinical pharmacokinetic and toxicology studies that have been conducted by Otonomy are sufficient to support an NDA filing. However, should unexpected findings occur in the clinic, further nonclinical studies may be requested.

Discussion: No further discussion was necessary.

1.7.2. Clinical

b. Does FDA concur with the 6 mg dose selection for OTO-201 and the sole use of sham control in the Phase 3 clinical studies?

FDA Response: It is unclear why you have chosen a dose of 6 mg when the Phase 1 study showed no differences between the 4 mg and 12 mg doses. We concur with the sole use of sham control in the Phase 3 clinical studies.

Discussion: Otonomy provided their rationale for the proposed dose of 6 mg. (b) (4) [redacted] A volume of 0.1 mL could generally be administered successfully. Otonomy noted that the proposed dose of 6mg in 0.1 mL is similar to the total dose administered for Ciprodex for 7 days. No further discussion was necessary.

c. Does the FDA concur with the proposed clinical development strategy and the selection of the primary efficacy endpoint that will support the NDA filing?

FDA Response: We concur with the proposed clinical development strategy. Regarding the primary efficacy endpoint, we have the following questions:

1) Why have you chosen otic treatment failure rather than treatment failure as defined in your Phase 1 study? Subjects who receive systemic antibiotics but who do not develop otorrhea should be counted as failures in the primary efficacy analysis using the ITT population; the most likely reason for systemic antibiotic administration in this population is acute otitis media.

Discussion: Originally, Otonomy planned to exclude systemic antibiotic use from the definition of treatment failure because most of the antibiotics prescribed in the Phase 1 trial were for reasons other than ear infection. The Division pointed out that conditions such as upper respiratory tract infection and sinus infection are associated with ear infection and that administration of systemic antibiotics might prevent the development of otorrhea in these patients. The Division recommended that Otonomy include the use of systemic antibiotics in the treatment failure definition for the primary analysis and exclude them in a sensitivity analysis.

2) The treatment failure definition includes prescription of otic antibiotic drops in patients who do not have otorrhea. What are diagnostic criteria for this?

Discussion: Otonomy explained that patients might be treated with otic drops in the absence of otorrhea if the tympanostomy tube was occluded or if a granuloma was present. The Division recommended that the specific reason for prescribing otic drops be included in the documentation on the case report form.

3) Why is treatment failure because of otorrhea defined as beginning on day 3 rather than earlier?

Discussion: Otonomy explained that there could be post-surgical drainage not related to infection up to three days after tube placement.

d. Does the FDA concur with the proposed clinical development strategy and requirement for number of subjects exposed to OTO-201 that will support the NDA filing?

FDA Response: We concur with the proposed clinical development strategy and with the plan for approximately 360 subjects to be exposed to OTO-201. Note that the sample size for each study may have to be changed based on the assumptions to make sure that the studies are powered sufficiently according to the revised endpoint.

In your proposed PK study 201-201304, you plan to evaluate the PK of OTO-201 in pediatric patients 4-12 years of age. Please provide a rationale for your proposal to evaluate the PK in these patients, given that the product will also be used in patients 6 months-2 years and patients >2 years.

Discussion: Otonomy plans to draft a request for a waiver of a bioavailability study since there is a large of amount of safety and PK information already available for ciprofloxacin and the dose being used is low.

e. Does the FDA concur with the proposed plan of testing hearing function in only subjects that are able to complete conventional audiometry?

FDA Response: We concur with the plan for audiometric testing in subjects 4 years of age and older. However, hearing function must also be evaluated in a subset of at least 30% of the younger children.

Discussion: The Division recommended a target of approximately 60 subjects less than age 4 years for evaluation of hearing function. Testing could be done at selected sites across both studies or in one study.

Additional comments:

1) The Division suggested that Otonomy investigate the time to onset of otorrhea post-surgery as an important secondary endpoint.

2) Since there is no single optimal way to deal with missing data in clinical trials, sponsors should make every attempt to limit loss of patients from the trial, even if it is 5%, as it can seriously impact the interpretation of the results. Missing observations can be informative and there are several approaches to assess the robustness of the results and these methods should be specified in the protocol as sensitivity analyses. The sensitivity analysis should include classifying the missing values as failures in the ITT population. We suggest that you may also

consider multiple imputation as an additional sensitivity analysis and any important baseline covariate(s) should be pre-specified.

Discussion: Otonomy asked if a Cochran-Mantel-Haenszel test for the primary analysis could be used due to the age stratification and the Division agreed. The Division recommended that the Z-test be used as a sensitivity analysis.

3) Otonomy was asked to provide definitions for analysis populations. The primary efficacy endpoint must be analyzed based on the ITT population, which consists of all-randomized patients.

Discussion: Otonomy confirmed that the primary efficacy endpoint will be based on the ITT population, which will consist of all randomized patients. Analysis population descriptions are included in the protocol.

4) Otonomy was asked to consider including a microbiological efficacy endpoint to assess the effectiveness of OTO-201. Bacteriology samples should be obtained for culture/identification and susceptibility testing at the Baseline visit for all subjects. At subsequent visits, bacteriology samples should also be collected from subjects who were deemed clinical failures. The following microbiology endpoint assessments should be considered:

- Microbiological response at End of Therapy
- Microbiological response at Follow-up

Discussion: The Division agreed with Otonomy's plan to obtain cultures at the following time points: baseline and at any study visit when otorrhea is present.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

Though not a specific issue requiring further discussion, the Division reminded Otonomy of the need to submit a Pediatric Study Plan within 60 days of the End-of-Phase 2 meeting. The plan should include information on why certain pediatric age groups would not be studied (e.g., less than 6 months or greater than 12 years.)

5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Meeting minutes will be provided within 30 days	FDA	October 9, 2013
Otonomy will submit a Pediatric Study Plan within 60 days of the End-of-Phase 2 meeting	Otonomy	November 98, 2013
Otonomy will submit a request for a waiver of the pharmacokinetic data	Otonomy	TBD

6.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts.

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

/s/

SUMATHI NAMBIAR
09/25/2013