

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207986Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: December 10, 2015
Requesting Office or Division: Division of Anti- Infective Products (DAIP)
Application Type and Number: NDA 207986
Product Name and Strength: Otiprio (ciprofloxacin otic suspension); 6 %
Submission Date: December 4, 2015 and December 8, 2015
Applicant/Sponsor Name: Otonomy
OSE RCM #: 2015-2141-1
DMEPA Primary Reviewer: Sevan Kolejian, PharmD
DMEPA Team Leader: Vicky Borders-Hemphill, PharmD

1 PURPOSE OF MEMO

Division of Anti- Infective Products (DAIP) requested that we review the revised container label, carton labeling and Instruction for Use (IFU) for Otiprio (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.¹

2 CONCLUSION

The revised container label, carton labeling and Instruction for Use (IFU) for Otiprio are acceptable from a medication error perspective.

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

¹ Kolejian, Sevan. Human Factor Study Result and Label and Labeling Review for Otiprio (NDA 207986), Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 DEC 1. OSE RCM No.: 2015-2141

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/s/

SEVAN H KOLEJIAN
12/10/2015

BRENDA V BORDERS-HEMPHILL
12/10/2015

505(b)(2) ASSESSMENT

Application Information		
NDA # 207986	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Otiprio Established/Proper Name: ciprofloxacin 6% otic suspension Dosage Form: otic suspension Strengths: 60 mg/mL (6%)		
Applicant: Otonomy, Inc.		
Date of Receipt: February 25, 2015		
PDUFA Goal Date: December 25, 2015	Action Goal Date (if different):	
RPM: Jane A. Dean, RN, MSN		
Proposed Indication(s): Treatment of middle ear effusion in pediatric patients with otitis media undergoing tympanostomy tube placement		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?
- YES ☐ NO ☒

If “YES” contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

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**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
NDA 019537	FDA's previous finding of safety (nonclinical)

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

- 3) The bridge in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug(s) or to justify reliance on information described in published literature for approval of the 505(b)(2) product. Describe in detail how the applicant bridged the proposed product to the listed drug(s) and/or published literature¹. [See also Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.](#)

The applicant is relying on prior findings of nonclinical safety for ciprofloxacin tablets (NDA 019537) to incorporate toxicity information for ciprofloxacin administered by the non-otic route in OTIPRIO.

The rationale for bridging OTIPRIO to CIPRO® (ciprofloxacin hydrochloride tablet) is that OTIPRIO and CIPRO® contain the same active pharmaceutical ingredient (API), namely ciprofloxacin free base, and nonclinical information regarding ciprofloxacin toxicity that is required for the NDA approval of OTIPRIO is contained in the CIPRO® product label.

The API for both CIPRO® and OTIPRIO is the same, ciprofloxacin free base, anhydrous, manufactured according to USP monograph requirements. Because OTIPRIO contains the same API as CIPRO®, and based the FDA's finding of safety and effectiveness for CIPRO®, nonclinical safety information pertaining to the API (ciprofloxacin free base) from the CIPRO® label should be acceptable as a source of information for the nonclinical safety information pertaining to the same API in OTIPRIO.

Information about the genetic toxicology of a particular API is required information for all NDA applications and required information on the product labels of all approved drugs containing the API. Specific information regarding ciprofloxacin genetic toxicity is derived from nonclinical studies that were conducted to support the approval of CIPRO®. Information regarding the results of these studies is contained in the CIPRO® product label, and the same information is required as part of the NDA application for OTIPRIO. In the absence of new study data or literature reports supplying this required nonclinical information, the CIPRO® labeling information is the source of the genetic toxicity data for ciprofloxacin needed to support the OTIPRIO NDA application.

¹For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s). Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies). A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s). For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product.

CIPRO® is an oral ciprofloxacin tablet with substantial systemic exposure, and OTIPRIO is an otic ciprofloxacin suspension with limited systemic exposure. However, the genetic toxicology assessment of a particular API is not dependent of the route, exposure, or the clinical dose of the API in any of the drugs where it is included. Regardless of its route or extent of exposure, a particular API is considered to have the same potential to produce mutations and/or chromosomal aberrations based on the results of a standard battery of nonclinical *in vitro* and *in vivo* genetic toxicology assays. Even though the ciprofloxacin in OTIPRIO does not distribute systemically to a large extent, it could still cause mutation or chromosomal aberrations in the middle ear, where it does distribute after otic administration, depending on the genetic toxicity potential of ciprofloxacin. The assessment of the genetic toxicity potential of ciprofloxacin is based on the results of nonclinical genetic toxicology studies conducted to support the NDA approval of CIPRO®. This important and required information which is available on the CIPRO® product label is equally valid for CIPRO® and OTIPRIO®.

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved as labeled without the published literature)?

YES ☐ NO ☒

If "NO," proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☐ NO ☐

If "NO," proceed to question #5.

If "YES", list the listed drug(s) identified by name and answer question #4(c).

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☐ NO ☐

¹For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s). Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies). A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s). For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product.

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☒ NO ☐

If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
Cipro Tablets	NDA 019537	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☒ YES ☐ NO ☐

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES ☐ NO ☒

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES ☐ NO ☒

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c) Described in a final OTC drug monograph?

YES ☐ NO ☒

If "YES", please list which drug(s).

Name of drug(s) described in a final OTC drug monograph:

- d) Discontinued from marketing?

YES ☐ NO ☒

If “YES”, please list which drug(s) and answer question d) i. below.

If “NO”, proceed to question #9.

Name of drug(s) discontinued from marketing:

- i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☐

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

- 9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsule to solution”).

This application provides for a new indication, treatment of pediatric patients with bilateral otitis media with effusion undergoing tympanostomy tube placement, and change in dosage form, from tablet to otic suspension. The application also provides a new route of administration, single intratympanic administration into affected ear(s) following suctioning of middle ear effusion.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

- 10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms intended for the same route of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; and **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA’s “Approved Drug Products with Therapeutic Equivalence Evaluations” (the Orange Book)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☐ NO ☒

If "**NO**" to (a) proceed to question #11.
If "**YES**" to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A ☐ YES ☐ NO ☐

If this application relies only on non product-specific published literature, answer "N/A"

*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*

*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES ☒ NO ☐

*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☒

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

N/A ☐ YES ☒ NO ☐

If this application relies only on non product-specific published literature, answer "N/A"

*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*

*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in*

the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

Cetraxal® (ciprofloxacin 0.2% solution) N021918

Ciprodex® (ciprofloxacin 0.3% and dexamethasone 0.1%) N021537

Cipro® HC (ciprofloxacin 0.2% and hydrocortisone 1%) N020805

PATENT CERTIFICATION/STATEMENTS

- 12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed ☒ *proceed to question #14*

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☐ NO ☐

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

- 14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☒ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s): 4,670,444 and 5,286,754

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

- ☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*
- ☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.
- ☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☐ NO ☐

If "NO", please contact the applicant and request the signed certification.

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

If "NO", please contact the applicant and request the documentation.

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

Note, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.

YES ☐ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval ☐

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/s/

JANE A DEAN
12/08/2015

LABEL & LABELING AND HUMAN FACTORS STUDY RESULTS REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	December 1, 2015
Requesting Office or Division:	Division of Anti- Infective Products (DAIP)
Application Type and Number:	NDA 207986
Product Name and Strength:	Otiprio (ciprofloxacin otic suspension); 6 %
Product Type:	Single ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Otonomy
Submission Date:	9/23/2015
OSE RCM #:	2015-2141
DMEPA Primary Reviewer:	Sevan Kolejian, PharmD
Human Factors Specialist:	Quynh Nhu Nguyen, MS
DMEPA Team Leader:	Vicky Borders-Hemphill, PharmD
Deputy Director:	Irene Chan, PharmD, BCPS

1 REASON FOR REVIEW

On September 23, 2015, Otonomy Inc. submitted the results from a human factors (HF) validation study and proposed labels and labeling for Otiprio (ciprofloxacin otic suspension) 6 % for intratympanic use (NDA 207986).¹ Otiprio will be provided in vials containing 1 mL of suspension with the strength of 60 mg per mL. The provider will prepare one or two 0.1 ml doses (6 mg) for administration of 0.1 ml in one or each ear, respectively. If two doses are required, they should be prepared in separate syringes from the same vial. The vial will have a fill volume of 1 mL leaving (b) (4) of overfill. During preparation of each dose, the provider will need to withdraw 0.3 ml from the vial, change the preparation needle to the blunt administration needle, prime the syringe to 0.1 mL, and then administer only 0.1 ml of the product to the affected ear(s). The product must be kept cold during preparation and held by the aluminum seal to prevent the suspension from changing to the gel phase prematurely.

The Division of Anti –Infective Products (DAIP) requested that DMEPA review the HF validation study results and proposed labels and labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information	A
Previous DMEPA Reviews	B
FDA Adverse Event Reporting System (FAERS)	N/A
Human Factors Study	C
ISMP Newsletters	N/A
Prescribing Information (FPI)	D
Labels and Labeling	E

N/A=not applicable for this review

¹ Otiprio (ciprofloxacin otic suspension) 6% will be administered post-myringotomy for the treatment of middle ear effusion in pediatric patients with otitis media undergoing tympanostomy tube placement.

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

3.1 HUMAN FACTOR SUMMATIVE TEST RESULTS ASSESSMENT

We evaluated the HF study results submitted on September 23, 2015. The study was conducted with 15 untrained participants [five Ear Nose and Throat (ENT) physicians and ten Operating Room (OR) nurses]. During the study, participants prepared doses for both a single ear and a bilateral myringotomy and tympanostomy tube placement in a mock operating theater. The study evaluated participants' ability to successfully prepare and administer the product and understanding proper storage and handling instructions. Please see the study details in Appendix C.

The study results showed multiple participants experiencing task failures across all critical tasks. We summarized the failures and analyses below:

1. Three nurse participants attached a shorter, smaller bore, sharp needle while preparing the syringes instead of the 20 G, 3" blunt administration needle. The participants indicated that in actual use, they expect the ENT physician to perform this task. As a result, the Applicant determined that these errors were due to study artifact. Since there were no ENT physicians who selected the wrong administration needle and the subjective assessment did not lead us to determine that further changes to the IFU are likely to further mitigate the risk for this error, we determined that no additional mitigations are needed at this time.
2. Two participants over shook the vial when mixing causing some minor foaming; However both participants were still able to successfully draw up the required volume. We consulted with DAIP team at the October 30th, 2015, labeling meeting. DAIP did not identify any concerns if the vials are over shaken when mixing. DMEPA determined that the instructions clearly state the time period for shaking the vial and how to hold the vial while shaking. However, we recommend bold the statement "**shake the vial 5 to 8 seconds**" for prominence. This revision will not require additional validation in a HF study.
3. Three nurse participants drew less than the recommended 0.3 ml from the vial for one or more syringes:
 - a. One nurse selected shorter, smaller bore preparation needle, which resulted in the drawing of a smaller volume. DMEPA determined that the appropriate final dose of 0.1 mL was provided in the syringe and has no additional recommendations.
 - b. Another nurse filled only one syringe to 0.6 mL instead of two syringes to 0.3 mL. DMEPA determined that this failure may be attributable to the practitioner's personal experience to avoid puncturing the vial more than one time to prevent coring. We recommend adding clarifying statement to step 5 to prompt the user to use the same vial to prepare the second dose such as "Repeat Steps 3 and 4, using the same vial, to prepare a second syringe for the other ear...". This revision will not require validation in another HF study.
 - c. The third nurse drew up on 0.2 mL because she thought that 0.3 mL was too excessive and that the goal was to draw enough into the syringe to remove any air bubbles. DMEPA determined that this may be attributable to medication preparation practices, and we determined that no additional mitigations are needed at this time.
4. Four participants experienced use issues priming:
 - a. Two participants did not prime the blunt administration needle. However, both participants demonstrated that they understood the requirement to prime, and stated that the priming would typically be done immediately before the injection and not during

- preparation.
- b. Two other participants reduced the volume in the syringe to 0.1 mL prior to switching to the blunt administration needle. The Applicant attributed the failure to the participants. We reviewed the IFU and determined that the IFU needs to call out the replacement of the administration needle to further mitigate the risk.
 5. Three failures occurred during the preparation of the second dose (bilateral administration only). Two failures are discussed in 3 above. The third failure described that the participant prepared two syringes for the adult single ear scenario. This participant attributed the error to habit and not product design. Given this single occurrence, we do not have any recommendation at this time.

In addition, during the knowledge assessment portion of the study, seven participants gave incorrect responses to the question: **What to Do If the Product Gels During Preparation**. Three participants said shaking would help, while five participants said the vial would need to be discarded. The correct response is to cool the product (e.g., by returning it to refrigeration). The Applicant determined that neither shaking nor discarding the vial poses a risk to a patient, although discarding the product is not desirable. DMEPA recommends adding the statement “If OTIPRIO thickens during preparation, place the vial back in refrigeration” by revising Step 1 of the IFU to read “Keep product cold during preparation. If OTIPRIO thickens during preparation, place the vial back in refrigeration.” This revision will not require additional validation in an HF study.

3.2 FULL PRESCRIBING INFORMATION (FPI)

Our review of the PI identified error-prone units of measure² that may lead to medication errors in the Dosage and Administration (see section 4.1).

3.3 CONTAINER LABEL, AND CARTON LABELING

We performed a risk assessment of the proposed container label, carton labeling, and Dosage and Administration, Dosage Forms and Strengths, and How Supplied Sections of the PI to identify additional deficiencies that may lead to medication errors. Our review of the container labels and carton labeling identified areas of needed improvement to increase clarity, prominence, and readability of important information (see section 4.2).

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that failures identified in the HF Study results may be mitigated with revisions to the IFU. These recommended revisions will not require additional validation in an HF study. We provide recommendations for the IFU in Section 4.1.

We determined that the proposed container labels, carton labeling, and PI can be improved to increase clarity, readability and prominence of important information to promote safe use of this product (see section 4.1 and 4.2).

If you have further questions or need clarifications, please contact Karen Townsend, OSE Project Manager, at 301-796-5413.

² ISMP’s List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015 [cited 2015 12 01]. Available from: <http://www.ismp.org/tools/errorproneabbreviations.pdf>

4.1 RECOMMENDATIONS FOR THE DIVISION

DMEPA concludes that the proposed PI is vulnerable to confusion which can lead to medication errors. We have provided a detailed summary below for review and consideration by DAIP. We advise the following recommendations be implemented prior to approval:

A. Full Prescribing Information

a. All Sections

1. Delete the statement (b) (4) throughout the document since this product (b) (4).

b. Dosage and Administration (Section 2)

1. Revise dosing instructions from “is intended for single-patient use (b) (4) (b) (4)” to read “is intended for single-patient use, discard unused portion.” for clarity.

c. Instruction For Use

1. In Step 1 (Preparation), revise the statement “Keep product cold during preparation.” to read as follows: “Keep product cold during preparation. If OTIPRIO thickens during preparation, place the vial back in refrigeration.” to improve user understanding of how to handle if the product thickens during preparation to promote safe and effective use of this product.
2. In step 2, to increase prominence and avoid over shaking of the product, bold the statement “**shake the vial 5 to 8 seconds.**” as two participants in the validation study shook the vial too vigorously causing the product to foam. Revise the Step 4 (Priming the Syringe) by separating replacing the needle and priming the syringe into an additional Step to mitigate failures noted in HF study as follows:

STEP 4 Replace with the Administration needle

Replace the needle with a 20-24G, 2-3 inch **blunt**, flexible needle to be used for administration.

STEP 5 Priming the Syringe

Prime the needle leaving a dose of 0.1 ml (0.1 cc).

3. Revise Step 5 (Preparing Second Dose for Bilateral Administration Only) to read Step 6 (Preparing Second Dose for Bilateral Administration Only) and revise to read “Repeat Steps 3, 4 and 5, using the same vial, to prepare a second syringe for the other ear and then dispose of the vial. Use a different syringe for each ear.”

d. Description (Section 11)

1. Remove trailing zeros³, revise the statement “with rubber stopper containing 1.0 ml.” to read “with rubber stopper containing 1 ml.” to prevent errors.

e. How Supplied/ Storage and Handling Section (Section 16)

1. Clarify the statement [REDACTED] (b) (4) to read “FOR INTRATYMPANIC USE ONLY. Otiprio should be stored 2-8° C until prior to use to prevent thickening during preparation”.
2. Remove trailing zeros⁴, revise the quantity statement “1.0 ml” to read “1 ml”, to prevent tenfold reading errors.

4.2 RECOMMENDATIONS FOR THE APPLICANT

We recommend Otonomy, Inc. implement and submit the revisions below prior to action being taken on NDA 207986.

A. General Comment

Update all labels and labeling to reflect the conditionally approved proprietary name, Otiprio.

B. Container Label

1. Relocate the strength presentation, “6%”, to appear immediately beneath the established name on the main display panel for improved readability and strength prominence.
2. Revise [REDACTED] (b) (4) statement to read “single-patient use vial – Discard Unused Portion”.
3. Remove trailing zero⁵, 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 improved clarity.

³ 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>

⁴ 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>

⁵ 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>

⁶ Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>

4. If space permits, consider adding 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)].

C. 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 ensure overfill is not reused: “(b) (4)” should be revised to read “1 ml single patient use vial, discard unused portion”. (Draft Guidance: Container and Carton, April 2013 (lines 465-472⁶).
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 increased prominence of this important information.
6. Revise the usual dose statement “Usual Dosage: 0.1 ml in each affected ear” to read “Usual Dosage: 0.1 ml in each affected ear. For Instruction for Use and Preparation: See Prescribing Information.” since safe use of the product is depended on Instructions for Use provided in the Prescribing Information.
7. For clarity, delete “(b) (4)” and revise the storage statement to read “Store at 2°C to 8°C (36°F to 46°F).” for consistency with the prescribing information recommended changes made by OPQ.

D. 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 increased prominence of this important information.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Ciprofloxacin Otic suspension 6% that Otonomy submitted on September 23, 2015.

Table 2. Relevant Product Information for Ciprofloxacin Otic suspension 6%	
Initial Approval Date	N/A
Active Ingredient	ciprofloxacin
Indication	Post-myringotomy for treatment of middle ear effusion in pediatric subjects with otitis media requiring tympanostomy tube placement.
Route of Administration	Intratympanic (Otic)
Dosage Form	Sterile suspension
Strength	6% (60 mg per vial)
Dose and Frequency	0.1 ml (6 mg) to each affected ear
How Supplied	one vial (60 mg/mL) suspension
Storage	stored at 2-8°C

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On June 9, 2015, we searched the L:drive and AIMS using the terms, Ciprofloxacin, to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified four previous reviews: RCM # 2011-423⁷, RCM #2014-26403⁸, RCM #2015-432⁹, RCM# 2015-328397¹⁰ and RCM #2015-596¹¹. The RCM #2015-432 and RCM #2015-596 contains relevant recommendations for label and labeling. We have incorporated these recommendations whenever applicable in this review.

⁷ Sheppard, Jacqueline, Proprietary Name Review for (b) (4) (Ciprofloxacin) Otic Suspension, 6% (IND 110244). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 JAN 20. OSE RCM No.: 2014-26403.

⁸ Winiarski, Aleksander, Proprietary Name Review for (b) (4) (Ciprofloxacin) Suspension Injection, 6% (IND 110244). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 AUG 26. OSE RCM No.: 2014-17054.

⁹ Kolejian, Sevan, Human Factor Study Protocol Review Ciprofloxacin sterile Otic Suspension 6% (IND 110244). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 MAY 13. OSE RCM No.: 2015-432.

¹⁰ Kolejian, Sevan, Proprietary Name Review for (b) (4) (ciprofloxacin otic Suspension), 6% (NDA 207986). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 JUN 18. OSE RCM No.: 2015-328397.

¹¹ Kolejian, Sevan, Label and Labeling Review for (b) (4) (ciprofloxacin otic Suspension), 60 mg per ml (NDA 207986). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 JUL 22. OSE RCM No.: 2015-596.

APPENDIX C. HUMAN FACTORS STUDY

Overview of the HF Study:

The Human Factors Summative Test evaluated whether users could successfully prepare Otiprio for administration following the preparation instructions outlined in the Full Prescribing Information. These steps include selection of appropriate syringes and needles, mixing the suspension, drawing up the necessary volume, and priming the administration needles.

Study design:

- Simulated-use test: Following a brief introduction to the product, fifteen prospective users (five ENT physicians and ten nurses) were asked to prepare doses for both a single and a bilateral myringotomy and tympanostomy tube placement in a mock operating theatre.
- Post Simulation Interview: Following preparation of the doses, participants were interviewed to confirm that they understood all key aspects of the product's use and to determine whether they encountered any difficulties understanding and following the instructions (that may not have been obvious to the investigator).
- Participants in the study did not receive an in-service.

Critical Tasks (excerpted from Applicant's submission):



(b) (4)

Task Performance:

Table 5 below summarizes participant performance across the steps required to prepare Otiprio, as reported by the Applicant.

- One of the nurses (N4) conveyed to the moderator during the study that she was tired and was just coming off of a long shift. The participant did have difficulties throughout, and made several errors both in preparing doses during the scenarios and in her answers to the Post- Simulation Interview questions. While she may not have provided the moderator with her full attention during the session, her data is included regardless.
- A second nurse (N6) indicated during the interview that while she worked in the OR supporting ENT procedures, she never prepared syringes. At her facility, syringes were prepared by surgical techs from within the sterile field. Although she admittedly lacked recent experience preparing syringes, her data is included as well.

Table 5. Participant performance when preparing OTO-201 doses.

Green = Successful completion of the task; Yellow = Successful completion but with use difficulties; Red = Critical use error made of task.

	Gather supplies	Shake the vial to mix the suspension	Draw up 0.3 mL	Prime admin needle	Prepare second dose	Doses prepared successfully
E1		Some foaming				3
E2						3
E3						3

	Gather supplies	Shake the vial to mix the suspension	Draw up 0.3 mL	Prime admin needle	Prepare second dose	Doses prepared successfully
E4						3
E5						3
N1						3
N2	Wrong admin needle					3
N3		Some foaming				3
N4	Wrong admin needle		Drew < 0.3 mL			2
N5			Drew < 0.3 mL			2
N6	Wrong admin needle		Drew < 0.3 mL	Primes, then switches needles		0
N7				Primes then switches needles		3
N8						3
N9						3
N10						3

- The final column in the table shows the number of syringes (out of three) that participants prepared correctly. Twelve of the fifteen participants were successful in preparing them for both the single ear scenario (one syringe) and bilateral ear scenario (two syringes). Some minor issues were observed. Several participants were unfamiliar with the 20G, 3" flexible blunt needles provided for the study, and three did not use them, choosing a more familiar, sharp needle as the administration needle instead. These participants said they expected the ENT would change administration needles at

their discretion. An ENT and a nurse participant shook the vial too vigorously and had some foaming of the suspension during preparation. But they otherwise prepared their doses successfully. Three nurses did not prime one or more administration needles, assuming that the ENT or surgical tech would prime just prior to administration. And one ENT did not prime, stating that he would do so only at the time of administration. None of these issues were considered critical use issues as all syringes would have yielded the target dose.

Three nurses (N4, N5, N6) made critical use errors and did not prepare all three doses correctly.

- N4 drew up 0.3 ml both syringes in the bilateral scenario, but did not prime the administration needle, assuming that the ENT would do so at the time of administration. On the single ear scenario however, she drew up only 0.1ml and left the administration needle unprimed. Priming would have yielded a dose somewhat less than 0.1ml, even with the shorter, smaller bore needle she selected as the administration needle. In the Post-Simulation Interview, she said she was confused about drawing up 0.3 ml while needing only 0.1ml.
- N5 completed the single ear scenario first, without issue. However, on the second, bilateral scenario, she became "fixated" (her word) on the need to use two syringes rather than drawing both doses into one syringe and administering those doses from the same syringe. She felt the latter approach would be safer, rather than needing to puncture the small OT0-201 vial twice with a lower gauge needle. In the end, she drew up only 0.1ml in a single syringe, before stopping.
- N6 thought drawing up 0.3 ml per dose was excessive; in her experience, 0.2 ml would be ample. She also primed the needle she used to draw up the suspension to 0.1 mL before switching to a new administration needle. This would have yielded a dose of less than 0.1ml. In the Post-Simulation Interview, she indicated she did not normally prep syringes and that her role would be to mix the suspension before handing the vial to a surgical tech, within the sterile field.
- A fourth nurse (N7) prepared three syringes correctly, but choose to prepare a second syringe for the adult, single ear scenario: In preparing the extra syringe, she drew 0.3 ml from the vial, but primed the syringe to 0.1ml before attaching the administration needle. This would have yielded a dose of less than 0.1ml.

Use Issues and Analysis of Root Cause provided by Applicant

Critical Task	Failures	Sponsor's root cause and rationale or proposed mitigation strategy
Step 1: Gather supplies	Three participants (N2,N4 and NG) did not use the 20G, 3" blunt administration needle provided with the supplies in the mock procedure room. Instead, these participants attached a shorter,smaller bore, sharp needle (e.g.,20G 1.5") while preparing the syringes.	<p>All participants correctly understood that the instructions were describing a blunt needle, but did not find the needle they were expecting, or assumed it would be changed later, prior to administration. This result is arguably an artifact of the simulated procedure room used in the study: the participants were not familiar with the supplies, or the arrangement of supplies. They would be familiar with the supplies in their own facilities. In addition, any administration needles preferred by physicians would be available and known to them.</p> <p>There are no recommendations to change the instructions for this step.</p>

<p>Step 2: Shake the vial to mix the suspension</p>	<p>Two participants (E1 and N3) shook the OT0-201a little too vigorously causing some minor foaming. While foaming can make preparing OT0-201 somewhat more difficult, both participants were able to successfully prepare full doses, as observed by the moderator.</p>	<p>Shaking a suspension to achieve a homogeneous mixture should strike a balance between shaking too vigorously and not shaking enough. The instructions state to shake the vial for five to eight seconds, and provide an illustration to convey how to hold the vial while shaking.</p> <p>Users will interpret how vigorously to shake based on their experience with other suspensions, as did participants in this study. The participants who shook hard enough to create some foaming were not surprised and assumed it was just the nature of the product, based on their experience with other medications. While foaming makes OT0-201 somewhat more difficult to draw up, the moderator observed that both participants who experienced foaming were still able to successfully draw up the required volume.</p> <p>There are no recommendations to change the instructions for this step.</p>
<p>Step 3: Draw up 0.3 ml</p>	<p>Three nurses (N4, N5, and N6) drew less than the recommended 0.3ml from the vial for one or more syringes: N5 filled only one needle in the bilateral scenario, N4 drew up less than 0.3ml in the single-ear scenario, and N6 drew up less than 0.3ml in both scenarios.</p>	<p>N4 stated she was nervous and this appeared to be a contributing factor, if not a cause of her error. She had also, in her words, worked a very long shift before attending the session.</p> <p>Another contributing factor may have been the choice of administration needle. As noted, a number of nurse participants (including N4) did not choose the 20G, 3" blunt flexible needle provided with the</p>

		<p>supplies in the mock procedure room, because they were not familiar with these needles. Instead, they chose a shorter, smaller bore needle. For these needles, a smaller volume would be sufficient to prime the needle and leave enough for a dose. This may have contributed to her puzzlement about why she needed to withdraw three times as much volume as she needed for the final dose. Had the participant chosen the longer needle, the rationale for the recommended volumes may have been more obvious to her.</p> <p>N5 was fixated on the direction to use a separate syringe for each dose. She felt that drawing both doses into a single syringe would be preferable. She also expected, given her experience, that a vial as small as the OT0-201 vial should only be accessed once: she was reluctant to puncture the vial septum with a second needle. By her own account, she was unable to get past these two issues. She eventually ended the task, without preparing either syringe.</p> <p>Like N4, N6 did not select the 3" blunt, flexible administration needle, choosing a 22G, 1.5" sharp needle instead. The 3" needles supplied for the study were not what she was expecting. She drew only 0.2 ml from the vial for each dose she prepared, less than the recommended 0.3 ml. She indicated that 0.3 ml was too</p>
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		<p>much, and that the goal was to draw enough into the syringe to remove any air bubbles. With a shorter, smaller gauge needle, drawing less volume into the syringe would be acceptable as there would still be ample volume for priming the smaller needle. In this case, she understood, but chose to ignore the direction in the instructions, relying on her professional experience instead.</p> <p>There are no recommendations to change the instructions for this step.</p>
Step 4: Replace with blunt needle and prime.	Replace with blunt needle (see above step 1)	<p>(see above step 1)</p> <p>There are no recommendations to change the instructions for this step.</p>
	<p>Priming:</p> <p>Overall, four participants experienced use issues priming the needle over the two scenarios.</p> <ul style="list-style-type: none"> • Two participants (E1 and N4) did not prime the administration needle. • Two participants (N6 and N7) reduced the volume in the syringe to 0.1ml prior to switching to the administration needle. 	<p>Priming:</p> <p>E1 and N4 did not commit a use error, per se. E1 had prepared the syringes correctly to that point in the procedure, and demonstrated in the Post-Simulation Interview that he understood the requirement to prime, and would have primed to 0.1ml just prior to administration. N4 had other issues, but understood the need to prime.</p> <p>For the participants that reduced the volume in the syringe to 0.1ml prior to attaching the administration needle, the root cause of the error differed. For N6, her relative lack of experience preparing syringes for injection may have</p>

		<p>contributed: she offered that she did not normally do this work at her facility- rather, surgical techs had responsibility for preparing syringe-based medications during surgical procedures. N7's error was caused by habit"- in her words, she would normally set the dose and then change the needle for administration. She subsequently prepared the two syringes for the bilateral scenario correctly. Reducing the volume in a syringe to the required dose volume before attaching an administration needle may be a reasonable practice with shorter, smaller bore needles typically of subcutaneous injections. Small bore needles take up little volume when primed. But this practice would lead to under dosing if the longer, larger bore administration needle were used (such as the needle recommended in the instructions).</p> <p>There are no recommendations to change the instructions for this step.</p>
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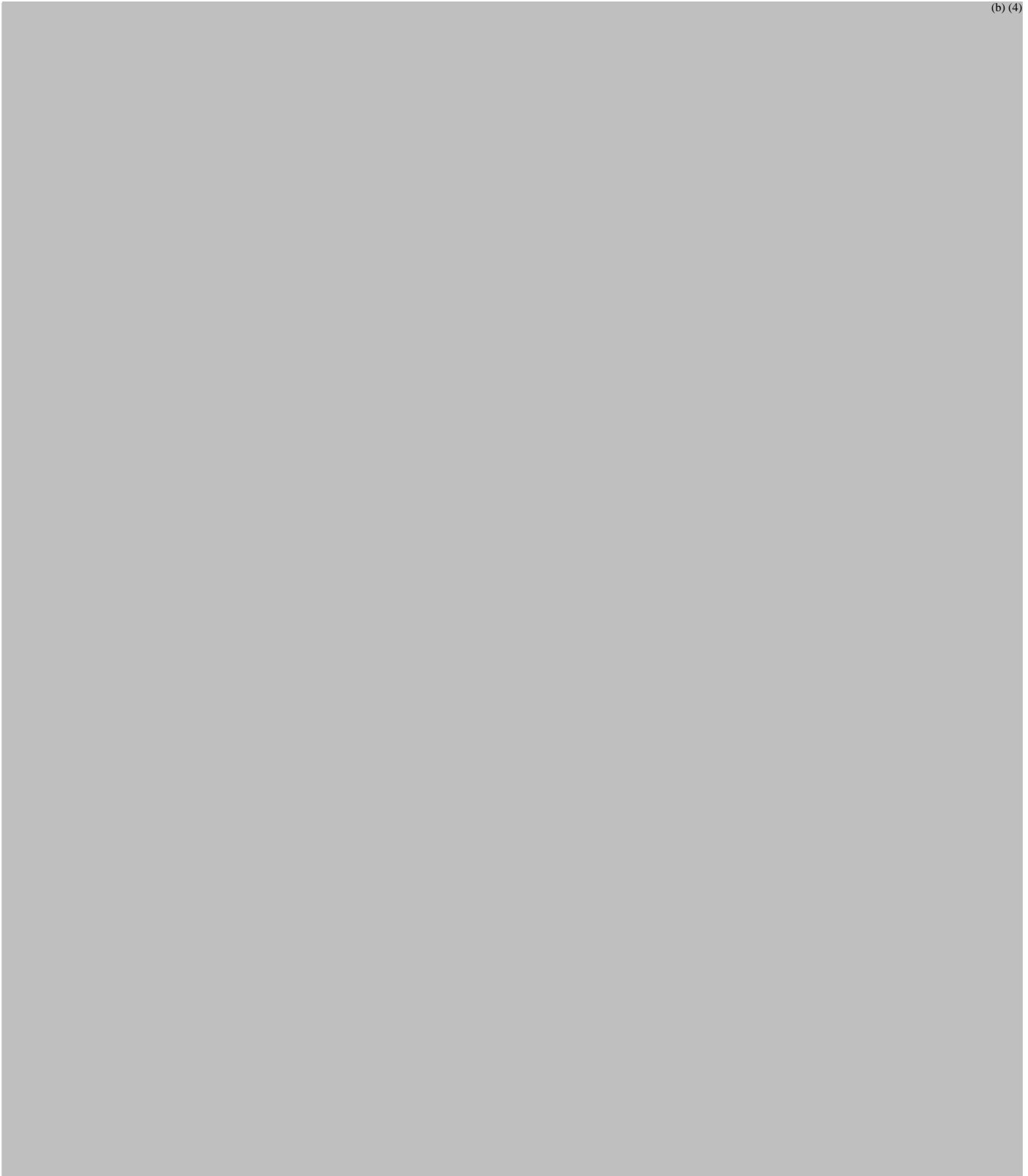
<p>Step 5: Prepare the second dose bilateral administration only)</p>	<p>N4 drew up 0.3 ml for both syringes in the bilateral scenario, but did not prime the administration needle.</p> <p>N5 completed the single ear scenario first, without issue. However, on the second, bilateral scenario, she became "fixated" (her word) on the need to use two syringes rather than drawing both doses into one syringe and administering those doses from the same syringe. She felt the latter approach would be safer, rather than needing to puncture the small OT0-201vial twice with a lower gauge needle. In the end, she drew up only 0.1ml in a single syringe, before stopping.</p> <p>A fourth nurse (N7) prepared three syringes correctly, but choose to prepare a second syringe for the adult, single ear scenario.</p>	<p>There are no recommendations to change the instructions for this step.</p> <p>There are no recommendations to change the instructions for this step.</p>
<p>Storage and Handling</p>	<p>Misunderstanding What to Do If the Product Gels During Preparation: During the Post-Simulation Interview, seven participants gave incorrect responses to the question {/What should you do if</p>	<p>Misunderstanding What to Do If the Product Gels During Preparation: In hindsight, the question posed may have been misinterpreted by these participants. The question asked "what should you do if OTIPRIO gels during preparations" differed from the related statement in the</p>

	<p>OTIPRIO gels during preparation?": three said shaking would help while five said the vial would need to be discarded. The correct response is to cool the product (e.g., by returning it to refrigeration). While neither shaking nor discarding pose a risk to a patient, discarding the product is clearly not desirable.</p>	<p>instructions "if OTIPRIO thickens during preparation, place the vial back in the refrigerator" (emphasis added}. For some, the word "gel" may have suggested an undesirable change to the underlying substrate, making the product unusable.</p> <p>There are no recommendations to change the instructions for this step.</p>
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The Applicant concluded:

Overall, no patterns of error emerged. In one instance, the error was detected by the participant, and subsequent syringes prepared successfully. In another, a participant prepared the first syringes correctly, but erred on her final syringe. Another participant chose to proceed based on her own experience, rather than strictly following the instructions. A fourth did not complete the bilateral scenario because she was confused by why each dose for a bilateral procedure would require a separate syringe.

Some other issues were observed, including two instances where vigorous shaking created some foaming, several nurses not recognizing (and not using) the longer ,blunt administration needle, and several participants assuming that the product should be discarded if it "gels" during preparation. However, these issues would not pose a risk to patients.



APPENDIX D. PRESCRIBING INFORMATION

APPENDIX D. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,¹² along with postmarket medication error data, we reviewed the following ciprofloxacin sterile otic suspension 6% labels and labeling submitted by Otonomy on September 23, 2015.

- Container label
- Carton labeling

G.2 Label and Labeling Images

1. Container label



2. Carton labeling

¹² Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

SEVAN H KOLEJIAN
12/01/2015

QUYNHNNHU T NGUYEN
12/01/2015

BRENDA V BORDERS-HEMPHILL
12/02/2015

IRENE Z CHAN
12/03/2015

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

******Pre-decisional Agency Information******

Memorandum

Date: November 18, 2015

To: Jane Dean
Regulatory Project Manager
Division of Anti-Infective Products (DAIP)

From: Adam George, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Amy Toscano, Pharm.D, RAC, CPA
Team Leader
Office of Prescription Drug Promotion (OPDP)

Subject: **NDA 207986 Otiprio (ciprofloxacin otic suspension) for intratympanic use**

This consult review is in response to DAIP's May 1, 2015, request for OPDP's review of the draft package insert (PI) and carton/container labeling for NDA 207986 Otiprio (ciprofloxacin otic suspension) for intratympanic use.

OPDP's review of the PI is based on the substantially complete version titled "NDA 207986 (Otiprio) SCPI Label 11-9-15 (marked up)" sent via email from Jane Dean to Adam George (OPDP) on November 11, 2015. OPDP's comments and edits to the proposed PI are included in the attached copy of the labeling. OPDP's review of the carton/container labeling is based on the version sent via email from Jane Dean to Adam George (OPDP) on November 18, 2015. OPDP does not have any comments on the carton/container labeling at this time.

OPDP appreciates the opportunity to provide comments on these materials. If you have any questions or concerns, please contact Adam George at 301-796-7607 or adam.george@fda.hhs.gov.

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/s/

ADAM N GEORGE
11/18/2015

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

CLINICAL INSPECTION SUMMARY

DATE: October 30, 2015

TO: Jane Dean, R.N., M.S.N., Regulatory Project Manager
Mark Needles, M.D., Medical Officer
Tom Smith, M.D., Clinical Team Leader
Sumathi Nambiar, M.D., M.P.H., Division Director
Division of Anti-Infective Products (**DAIP**)

FROM: John Lee, M.D., Medical Officer
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations (**OSI**)

THROUGH: Janice Pohlman, M.D., M.P.H., Team Leader
Kassa Ayalew, M.D., M.P.H., Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation, OSI

SUBJECT: Evaluation of Clinical Inspections

APPLICATION: NDA 207986

APPLICANT: Otonomy, Inc.
Barbara M. Finn, Vice President
Regulatory Affairs and Quality Assurance
(858) 242-5238; bfinn@otonomy.com

DRUG: Ciprofloxacin (b) (4) Otic Suspension (propriety name pending)

NME: No

INDICATION: Treatment of middle ear effusion in pediatric patients with otitis media undergoing tympanostomy tube placement

REVIEW CLASSIFICATION: Standard Review

APPLICATION SUBMISSION DATE: February 25, 2015

DARRTS CONSULTATION DATE: April 27, 2015

INSPECTION SUMMARY GOAL DATE: November 1, 2015

REGULATORY ACTION GOAL DATE: December 11, 2015

PDUFA DUE DATE: December 25, 2015

I. BACKGROUND

In this NDA 207986, Otonomy, Inc. (**Otonomy**) references NDA 019537 for Cipro® in seeking 505(b)(2) approval of Ciprofloxacin (b) (4) Otic Suspension (propriety name pending) for the treatment of middle ear effusion in pediatric patients with otitis media (**OM**) undergoing tympanostomy tube placement.

In the United States (**US**), children are treated with antibiotics most commonly for OM, typically caused by *Streptococcus pneumoniae*, *Haemophilus influenza*, or *Moraxella catarrhalis*. Acute OM usually resolves (with or without oral antibiotics) but one-third of cases may progress to chronic and/or recurrent OM with effusion, irreversible hearing loss, delays in speech and language, and in extreme cases, even mastoiditis or meningitis. Chronic recurrent OM is often managed surgically with myringotomy, aspiration of middle ear effusion, and tympanostomy tube placement (**TTP**).

Over one million TTP are performed each year and most are successful, but many children develop post-TTP otorrhea. Antibiotic drops are routinely used post-TTP (off-label topical use), and used repeatedly since the drops rapidly drain via the eustachian tube. OTO-201 is a poloxamer formulation for sustained-release of ciprofloxacin active against all major bacteria in OM. OTO-201 administered once intra-operatively at TTP may eliminate the need for repeated post-TTP off-label topical use of antibiotic drops, and potentially also improve post-TTP outcome.

Of the new studies sponsored by Otonomy (under IND 110244), the two pivotal Studies OTO-201-201302 (**Study 302**) and OTO-201-201303 (**Study 303**) were audited at good clinical practice (**GCP**) inspections of four clinical investigator (**CI**) sites selected for large site subject enrollment. Both studies were audited at one CI site for a total of five study-sites, three for Study 302 and two for Study 303. The two studies (identical title/design) are briefly described below.

Studies 302 and 303

A Prospective, Randomized, Double-blind, Sham-controlled, Multicenter, Phase 3 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 two identical Phase 3, randomized, double-blind, sham-controlled studies were conducted in parallel between November 2013 and June/May 2014 with 266 subjects randomized in each study, at 29 CI sites (25 US and four Canada) in Study 302 or at 19 CI sites (18 US and one Canada) in Study 303. The primary objective was to confirm the effectiveness of OTO-201 in the treatment of pediatric subjects with bilateral middle ear effusion who require TTP.

Subject Inclusion

- Boys or girls of age 6 months to 17 years
- Bilateral OM with effusion requiring TTP
- Able to provide assent
- Caregiver able to provide informed consent and comply with all study requirements

Subject Exclusion

- History of prior ear or mastoid surgery, except myringotomy with or without TTP
- Anticipated surgery concurrent with TTP (e.g., adenoidectomy or tonsillectomy)
- Sensorineural hearing loss
- Tympanic membrane perforation
- History of infections and likely requirement for antibiotic therapy during study
- Abnormal tympanic membrane/middle ear that may complicate intra-tympanic injection (**ITI**)
- Use of topical non-steroidal otic agents within one day
- Use of topical or otic corticosteroids within three days
- Use of systemic corticosteroids within seven days

- Presence of any infection requiring systemic antimicrobial/antifungal agents
- Use of amoxicillin, Augmentin®, Omnicef®, ceftriaxone, and cephalexin within three days
- Use of doxycycline and fluoroquinolones within seven days
- Use of Zithromax® within 14 days
- Concurrent use of oral anti-inflammatory agents
- Known immune deficiency
- Previous exposure to OTO-201 or hypersensitivity to any of component of OTO-201
- Unable to complete all study evaluations, except audiometry if younger than four years old
- Use of an investigational drug or device within the last month
- Sibling of another participating subject or non-sibling residing in same household
- Menarchal or post-menarchal
- Any condition that complicates study participation

Treatment Groups and Regimen

- Randomization 2/1 OTO-201/sham, stratified by age (two years or younger, over two years)
- One dose of the study medication, ITI at TTP by an unblinded (empty syringe) otolaryngologist
- Active: OTO-201, ciprofloxacin 6 mg in 0.100 mL of poloxamer solution (6% ciprofloxacin)
- Sham treatment: empty 1.0 mL syringe (no placebo drug)

Major Endpoints and Analyses

Subjects were evaluated on post-operative Days 4, 8, 15, and 29 (Visits 3-6). Subjects with visible otorrhea on external examination could receive Ciprodex® four drops twice daily for seven days. During myringotomy, middle ear effusions were cultured prior to intra-operative ITI.

- Primary endpoint/analysis: comparison of OTO-201 and sham for proportion of subjects failing study treatment through Day 15 using Cochran-Mantel-Haenszel and chi-square tests, with treatment failure (TF) defined as any of the following:
 - Otorrhea in any ear on or after Day 4, documented by the blinded assessor
 - Any post-surgical use of a systemic or otic (drops) antibiotic
 - Unknown treatment response status, including missed visit or lost to follow up
- Secondary endpoints/analyses: (1) comparison of OTO-201 and sham for time to TF; (2) TF subject proportions through non-primary time points Days 4, 8, and 29; and (3) subject proportions with:
 - TF by otorrhea and/or antibiotic use through Days 4, 8, 15, and 29
 - Otorrhea-only TF through Day 15
 - Microbiologic TF through Days 15 and 29
- Safety monitoring: adverse events (AEs), otoscopy, tympanometry, audiometry, vital signs, physical examination, and laboratory tests

Sponsor-Reported Outcome

- Relative to sham, OTO-201 reduced the age-adjusted TF rate to about one-half: $p < 0.001$ (both studies), relative risk 0.55/0.46 (Study 302/303), and odds ratio 0.39/0.30 (Study 302/303).
- Relative to sham, OTO-201 ITI efficacy was statistically significant for the younger age stratum (six months to two years): $p = 0.005$ or < 0.001 (Study 302/303) and odds ratio 0.39/0.20 (Study 302/303).
- OTO-201 ITI was safe and well-tolerated. Treatment-emergent AEs (TEAEs) were similar for OTO-201 and sham, mostly mild or moderate and reported by about one-half of the subjects.
- No deaths or serious TEAEs were observed. Significant trends were not identified for audiometry, otoscopy, tympanostomy tube patency, laboratory testing, or physical examination.

II. INSPECTIONS

The following four CI sites in Studies 302 and 303 were identified for GCP inspection based on large subject enrollment. No special concerns were identified at NDA review for either study.

	Clinical Investigator Site	Study, Site, Enrollment	Inspection Dates & Outcome
1	John F. Ansley, M.D. 832 Cook Road Orangeburg, South Carolina	Study 303, Site 002, 32 subjects	July 7-9, 2015: NAI
2	David A. Evans, M.D. 1111 Exposition Boulevard Sacramento, California	Study 302, Site 080, 15 subjects	July 20-22, 2015: VAI
3	Eric A. Mair, M.D. 6035 Fairview Road Charlotte, North Carolina	Study 302, Site 079, 76 subjects	July 20-27, 2015: NAI
4	Donald V. Welsh, M.D. 4004 Dupont Circle, Suite 220 Louisville, Kentucky	Study 302, Site 051, 7 subjects Study 303, Site 051, 16 subjects	May 28 - June 2, 2015: NAI

NAI = no action indicated (no significant violations); VAI = voluntary action indicated (minor violations)

1. John F. Ansley, M.D.

a. What was inspected:

- Records review: study conduct including institutional review board (**IRB**) and sponsor oversight of study conduct, CI financial disclosure, drug accountability and disposition, and subject records
- Subject records: subject screening and eligibility evaluation, informed consent, treatment compliance, AEs and safety monitoring, and data verification
- Data verification: randomization, major efficacy endpoints, AEs, protocol deviations, subject discontinuations, and concomitant medication use

b. General observations and comments:

Study 303, Site 002: 34 subjects were screened, 34 were enrolled (randomized), and 32 completed the study. Case records were reviewed for all subjects, including detailed review for 16 enrolled subjects.

No significant deficiencies were observed and a Form FDA 483 was not issued. The following minor, apparently isolated protocol deviations appeared unlikely to be significant and were verbally discussed:

- Physical examinations (with or without tympanometry) were occasionally not performed, incomplete, or performed outside the protocol-specified time window (all deviations reported to sponsor).
- Subject 603-5 received active treatment in error (randomized to sham). Per sponsor instruction, the subject was assigned to active treatment and remained in the study.

Study conduct at this CI site appeared adequate, including IRB/sponsor oversight of study conduct. Study records were well maintained. All audited data were verifiable among source records, electronic case report forms (**eCRFs**), and NDA data listings.

c. Assessment of data integrity: The data from this study site appear reliable.

2. David A. Evans, M.D.

a. What was inspected:

- Records review: study conduct including IRB/sponsor oversight of study conduct, CI financial disclosure, drug accountability and disposition, and subject records
- Subject records: subject screening and eligibility evaluation, informed consent, treatment compliance, AEs and safety monitoring, and data verification
- Data verification: randomization, major efficacy endpoints, AEs, protocol deviations, subject discontinuations, and concomitant medication use

b. General observations and comments:

Study 302, Site 080: 21 subjects were screened, 15 were enrolled (randomized), and 15 completed the study. Case records were reviewed for all subjects, including detailed review for all enrolled subjects. The following deficiencies were observed, either cited on Form FDA 483 or verbally discussed:

Form FDA 483

- Minor isolated discrepancies between source records and eCRF:
 - Subject 212-6: Ciprodex® discontinuation date, discrepant by six days
 - Subject 219-3: AE (tonsillitis) resolution date, discrepant by two days
 - Subject 206-4: AE (cold) inadequately documented on source, not reported on eCRF
- For 10 (of 15) subjects enrolled, 13 medications used (mostly) prior to study enrollment (19 instances) were not reported to the sponsor (on eCRFs). On source records, the route and dates of use were typically not documented. For many of these medications (antibiotics and corticosteroids), the subject was to be excluded per protocol for use within 1-14 days (depending on medication/route).
 - Antibiotics: amoxicillin, azithromycin, cefdinir, and neomycin / polymyxin B / hydrocortisone
 - Corticosteroids: beclomethasone, budesonide, fluticasone, and mometasone
 - Other medications: acetaminophen, albuterol, cough syrup, diphenhydramine, and loratidine

OSI Comments: The overall context of this finding suggested that these medications (mostly prior to study) were permitted per protocol but not documented as permitted use, including in the sponsor's monitoring notes. The following examination nonetheless explores antibiotic use as protocol violations (worst case scenario as potential efficacy confounder), given the primary endpoint of treatment failure through Day 15 including any non-study antibiotic use, systemic or otic:

Subject	Group	TF-15	Antibiotic	Efficacy Outcome and NDA Approvability
206-4	sham	yes	concomitant azithromycin	treatment failure with or without azithromycin, no impact on NDA approvability
209-2	sham	no	prior cefdinir	treatment success for sham, cefdinir use unfavorable to NDA approvability
207-0	OTO-201	no	prior amoxicillin and Cortisporin®	treatment success for OTO-201 possibly due to non-study antibiotic use, favorable to NDA approvability
221-9	OTO-201	no	prior amoxicillin	

TF-15 = treatment failure at Day 15; Cortisporin® = neomycin / polymyxin B / hydrocortisone

Even if this observation reflects inadequate recordkeeping AND protocol violations: (1) the deficiency appears to be random (sham and OTO-201); (2) the amount of significantly affected data appears to be limited; and (3) overall, the deficiency does not appear to favor NDA approvability.

Verbal Discussion

- Five drops of Ciprodex® given per CI discretion, four drops specified in the protocol
- One instance of not completing an eCRF for an unscheduled visit
- Subject 212-6, unclear documentation of randomization code versus subject identification numbers
- Subject eligibility (inclusion and exclusion criteria) not always clearly documented
- Not removing an unqualified study investigator in a timely manner

All observed deficiencies appear minor, isolated, or otherwise unlikely to be significant to NDA review. Study conduct at this CI site appeared adequate overall, including IRB/sponsor oversight of study conduct. All audited data were verifiable among source records, eCRFs, and NDA data listings.

- c. Assessment of data integrity: The data from this study site appear reliable.

3. Eric A. Mair, M.D.

- a. What was inspected:

- Records review: study conduct including IRB/sponsor oversight of study conduct, CI financial disclosure, drug accountability and disposition, and subject records
- Subject records: subject screening and eligibility evaluation, informed consent, treatment compliance, AEs and safety monitoring, and data verification
- Data verification: randomization, major efficacy endpoints, AEs, protocol deviations, subject discontinuations, and concomitant medication use

- b. General observations and comments:

Study 302, Site 079: 81 subjects were screened, 76 were enrolled (randomized), and 76 completed the study. Case records were reviewed in detail for 12 enrolled subjects.

No significant deficiencies were observed and a Form FDA 483 was not issued. Study conduct at this CI site appeared adequate, including IRB/sponsor oversight of study conduct. Study records were well maintained. All audited data were verifiable among source records, eCRFs, and NDA data listings.

- c. Assessment of data integrity: The data from this study site appear reliable.

4. Donald V. Welsh, M.D.

- a. What was inspected:

- Records review: study conduct including IRB/sponsor oversight of study conduct, CI financial disclosure, drug accountability and disposition, and subject records
- Subject records: subject screening and eligibility evaluation, informed consent, treatment compliance, AEs and safety monitoring, and data verification
- Data verification: randomization, major efficacy endpoints, AEs, protocol deviations, subject discontinuations, and concomitant medication use

- b. General observations and comments:

Study 302, Site 051: Eight subjects were screened, seven were enrolled (randomized), and seven completed the study. Subject case records were reviewed in detail for all subjects.

Study 303, Site 051: 17 subjects were screened, 16 were enrolled (randomized), and 16 completed the study. Case records were reviewed for all subjects, including detailed review for 12 enrolled subjects.

No significant deficiencies were observed and a Form FDA 483 was not issued. The following minor, apparently isolated observations were verbally discussed:

Study OTO 201-201302

- ☐ Subject 201-7: Inaccurate rounding of Visit 6 tympanometry scores on eCRF
- ☐ Subject 202-8: Incomplete source documentation of Visit 1 audiometry score

Study OTO 201-201303

- ☐ Subject 613-3: Microbiology culture results not documented as part of subject records
- ☐ Subject 615-8: Inadequate source documentation of sevoflurane use (for surgical anesthesia)
- ☐ Subject 601-2: Inadequate reporting of sevoflurane use (not shown on eCRF)

Study conduct appeared adequate for both studies, including IRB/sponsor oversight of study conduct. All audited endpoint data were verifiable among source records, eCRFs, and NDA data listings.

c. Assessment of data integrity: The data from this study site appear reliable.

III. OVERALL ASSESSMENT AND RECOMMENDATIONS

In this 505 (b)(2) NDA 207986, Otonomy seeks approval of Ciprofloxacin (b) (4) Otic Suspension for the treatment of middle ear effusion in pediatric patients with OM undergoing TTP. Of the new studies sponsored by Otonomy, two pivotal studies of identical design (randomized, double-blinded, sham-controlled) were audited at GCP inspections of four CI sites selected for large site subject enrollment (146 combined, 27% of total 532). At each of the four CI sites, subject case records were reviewed for nearly all enrolled subjects, including detailed review for 62 subjects (12% of total 532).

At three CI sites, no significant deficiencies were observed and a Form FDA 483 was not issued. At Site 080 in Study 302 (Evans), a Form FDA 483 was issued for minor isolated discrepancies between source records and eCRF and repeatedly not reporting to the sponsor the use of concomitant medications. The unreported medications included antibiotics potentially important to the primary endpoint, but a significant impact on the overall study outcome appeared unlikely, given the limited amount of affected data. Overall, the study conduct appeared adequate at all four CI sites, including the sponsor's oversight of study conduct. All audited study data were adequately verifiable and appear reliable as reported in the NDA.

{See appended electronic signature page}

John Lee, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Janice K. Pohlman, M.D., M.P.H.
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/s/

JONG HOON LEE
10/30/2015

JANICE K POHLMAN
10/30/2015

KASSA AYALEW
10/31/2015

Division of Anti-Infective Products

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: NDA 207986

Name of Drug: Otiprio (Ciprofloxacin (6% ciprofloxacin (b) (4) otic suspension), 60 mg/mL

Applicant: Otonomy, Inc.

Labeling Reviewed

Submission Date: February 25, 2015

Receipt Date: February 25, 2015

Background and Summary Description:

Otonomy, Inc. has submitted a new drug application under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Ciprofloxacin (6% ciprofloxacin (b) (4) otic suspension), 60 mg/mL with the following indication: treatment of middle ear effusion in pediatric patients with otitis media undergoing tympanostomy tube placement.

Review

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the Selected Requirements for Prescribing Information (SRPI) checklist.

Recommendations

SRPI format deficiencies were identified in the review of this PI. All SRPI format deficiencies of the PI were conveyed to Otonomy, Inc. in the 74-day Filing Issues letter sent May 7, 2015. Otonomy was asked to correct these deficiencies and resubmit the PI in Word format by May 29, 2015. Otonomy submitted a revised label May 28, 2015.

Jane A. Dean, RN, MSN	July 14, 2015
Regulatory Project Manager	Date
Frances V. LeSane	July 14, 2015
Chief, Project Management Staff	Date

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/s/

JANE A DEAN
08/27/2015

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	July 22, 2015
Requesting Office or Division:	Division of Anti- Infective Products (DAIP)
Application Type and Number:	NDA 207986
Product Name and Strength:	Otiprio (ciprofloxacin otic suspension) 60 mg/mL
Product Type:	Single ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Otonomy
Submission Date:	2/25/2015
OSE RCM #:	2015-596; 2015-432
DMEPA Primary Reviewer:	Sevan Kolejian, PharmD
DMEPA Team Leader:	Vicky Borders-Hemphill, PharmD

1 REASON FOR REVIEW

This review evaluates the revised Human Factors Study Protocol and revised Instructions for Use (IFU) for Otiprio ciprofloxacin otic suspension 60 mg/mL submitted to NDA 207986 on June 15, 2015 in response to DMEPA recommendations provided in OSE review (RCM 2015-432)¹, dated May 13, 2015. Also, we evaluate container label, carton labeling, and Prescribing Information (PI) submitted on February 25, 2015. The Division of Anti –Infective Products (DAIP) requested that DMEPA review the revised Human Factors Study and revised IFU, and proposed labels and labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information	A
Previous DMEPA Reviews	B
FDA Adverse Event Reporting System (FAERS)	N/A
Human Factors Study	C
ISMP Newsletters	N/A
Other: Prescribing Information	D
Labels and Labeling	E

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Revised Human Factors Protocol and Instructions for Use

We evaluated the revised Otiprio Human Factors Study Protocol and revised IFU (Appendix C) submitted by the Applicant in response to DMEPA's previous comments in OSE RCM 2015-432, dated May 13, 2015 to assess whether the revisions adequately address our concerns. The Applicant adequately addressed all of DMEPA's concerns from a medication error perspective.

¹ Kolejian, S. Human Factors Study Protocol Review ciprofloxacin otic suspension (IND 110244). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 May 13. 6 p. OSE RCM No.: 2015-432.

Labels and Labeling

We performed a risk assessment of the proposed container label, carton labeling, and Dosage and Administration, Dosage Forms and Strengths, and How Supplied Sections of the PI to identify deficiencies that may lead to medication errors and areas for improvement.

Our review of the container labels and carton labeling identified areas of improvement to increase clarity, prominence, and readability of important information. We note that the proprietary name Otiprio was determined to be conditionally acceptable on July 8, 2015 and that the proprietary name Proauric was denied in January 20, 2015 and provided recommendation to add the proprietary name on container labels and carton labeling (see Section 4.2). Our review of the PI identified error-prone abbreviations and symbols, expression of units of measure that may pose confusion to the prescriber and needed improvements in the Dosage and Administration (see section 4.1).

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the Applicant adequately addressed all of DMEPA's concerns for the Human Factors protocol and IFU from a medication error perspective. However, we determined that the proposed container labels, carton labeling, and PI can be improved to increase clarity, readability and prominence of important information to promote safe use of this product.

If you have further questions or need clarifications, please contact Karen Townsend, OSE Project Manager, at 301-796-5413.

4.1 RECOMMENDATIONS FOR THE DIVISION

DMEPA concludes that the proposed PI is vulnerable to confusion which can lead to medication errors. We have revised the *Dosage and Administration* section of the Full Prescribing Information (See Appendix C) and have provided a detailed summary below for review and consideration by DAIP. We advise the following recommendations be implemented prior to approval:

A. Full Prescribing Information

a. All Sections

1. Revise the established name “([REDACTED])” to read “(ciprofloxacin otic suspension)” throughout the document. (b) (4)

b. Dosage and Administration Section

1. Revise dosing instructions from “is intended for single-patient use (b) (4)” to read ““is intended for single-patient use.” for clarity.
2. Revise dosing instructions from (b) (4) to read “given as intratympanic administration of 0.1 ml (6 mg) dose into affected ear. For bilateral tympanostomy tube placement, give 0.1 ml (6 mg) dose into each ear.” to clarify the dose for bilateral use.
3. To promote safe and correct dose administration of this product, move Direction for Use Figure 2 from the end of the section 16 to Dosage and Administration Section and title it as section 2.1 (see Appendix C)

c. Dosage Forms and Strengths Section

1. (b) (4)

d. How Supplied/ Storage and Handling Section

1. Clarify the statement (b) (4) to read “FOR INTRATYMPANIC USE ONLY. Otiprio should be stored 2-8° C until prior to use to prevent thickening during preparation”.

4.2 RECOMMENDATIONS FOR THE APPLICANT

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 word “(b) (4)” to read the approved proprietary name “Otiprio”
2. Revise the established name from “(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.
3. Relocate the strength presentation, “(b) (4)”, to appear immediately beneath the established name on the main display panel.
4. Remove the statement “(b) (4)”

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)].
6. Revise “(b) (4)” statement to read “single- patient use vial”
7. Relocate the quantity statement “1 mL” to appear in the upper right corner of the main display panel.

b) Carton labeling

1. See A.1 above
2. See A.2 above
3. See A.3 above
4. See A.4 above
5. See A.5 above
6. Relocate the statement, “FOR INTRATYMPANIC USE ONLY”, from the side panel to appear on the main display panel for prominence of important information
7. Revise the usual dose statement (b) (4) to read “Usual Dosage: 0.1 ml in each affected ear, See Prescribing Information” since safe use of the product is depended on Instruction for Use provided in Prescribing Information.
8. Revise the quantity statement from using an error prone trailing zero and to provide important overfill information “(b) (4)” to read “1 ml single patient use vial discard unused portion”. (Draft Guidance: Container and Carton, April 2013 (lines 469-472)).

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Ciprofloxacin sterile Otic suspension 60 mg/mL that Otonomy submitted on February 18, 2015.

Table 2. Relevant Product Information for Ciprofloxacin sterile Otic suspension 60 mg/mL	
Initial Approval Date	N/A
Active Ingredient	ciprofloxacin
Indication	Treatment of middle ear effusion in pediatric subjects with otitis media requiring tympanostomy tube placement.
Route of Administration	Intratympanic (Otic)
Dosage Form	Sterile suspension
Strength	6% (60 mg per vial)
Dose and Frequency	0.1 ml (6 mg) to each affected ear
How Supplied	one vial (60 mg/mL) suspension
Storage	stored at 2-8°C

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On June 9, 2015, we searched the L:drive and AIMS using the terms, Ciprofloxacin, to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified three previous reviews: RCM # 2011-423², RCM #2014-26403³ and RCM #2015-432⁴. The most recent review (RCM #2015-432) for Human Factor Study Protocol Review Ciprofloxacin sterile Otic Suspension 6% (IND 110244) contains relevant recommendations for label and labeling. We have incorporated these recommendations whenever applicable in this review.

² Sheppard, Jacqueline, Proprietary Name Review for (b) (4) (Ciprofloxacin) Otic Suspension, 6% (IND 110244). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 JAN 20. OSE RCM No.: 2014-26403.

³ Winiarski,Aleksander, Proprietary Name Review for (b) (4) (Ciprofloxacin) Suspension Injection, 6% (IND 110244). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 AUG 26. OSE RCM No.: 2014-17054.

⁴ Kolejian, Sevan, Human Factor Study Protocol Review Ciprofloxacin sterile Otic Suspension 6% (IND 110244). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 MAY 13. OSE RCM No.: 2015-432.

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/s/

SEVAN H KOLEJIAN

07/23/2015

BRENDA V BORDERS-HEMPHILL

07/23/2015

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 207986	NDA Supplement #: S-	Efficacy Supplement Category: <input type="checkbox"/> New Indication (SE1) <input type="checkbox"/> New Dosing Regimen (SE2) <input type="checkbox"/> New Route Of Administration (SE3) <input type="checkbox"/> Comparative Efficacy Claim (SE4) <input type="checkbox"/> New Patient Population (SE5) <input type="checkbox"/> Rx To OTC Switch (SE6) <input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7) <input type="checkbox"/> Animal Rule Confirmatory Study (SE7) <input type="checkbox"/> Labeling Change With Clinical Data (SE8) <input type="checkbox"/> Manufacturing Change With Clinical Data (SE9) <input type="checkbox"/> Pediatric
Proprietary Name: Established/Proper Name: ciprofloxacin 6% (b) (4) otic suspension Dosage Form: otic suspension Strengths: 60 mg/mL (6%)		
Applicant: Otonomy, Inc. Agent for Applicant (if applicable):		
Date of Application: February 25, 2015 Date of Receipt: February 25, 2015 Date clock started after UN:		
PDUFA Goal Date: December 25, 2015		Action Goal Date (if different):
Filing Date: April 26, 2015		Date of Filing Meeting: April 13, 2015
Chemical Classification (original NDAs only) : <input type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination <input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination <input type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination <input type="checkbox"/> Type 4- New Combination <input checked="" type="checkbox"/> Type 5- New Formulation or New Manufacturer <input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA <input type="checkbox"/> Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s): Treatment of middle ear effusion in pediatric patients with otitis media undergoing tympanostomy tube placement		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 .		

Type of BLA		<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)		
<i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i>				
Review Classification:		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority		
<i>The application will be a priority review if:</i> <ul style="list-style-type: none"> <i>A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)</i> <i>The product is a Qualified Infectious Disease Product (QIDP)</i> <i>A Tropical Disease Priority Review Voucher was submitted</i> <i>A Pediatric Rare Disease Priority Review Voucher was submitted</i> 		<input type="checkbox"/> Pediatric WR <input type="checkbox"/> QIDP <input type="checkbox"/> Tropical Disease Priority Review Voucher <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher		
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>		
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)		
<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:		<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B) <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)		
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): IND 110244				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the established/proper and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

system.				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If yes, explain in comment column.				
If affected by AIP , has OC/OMPQ been notified of the submission? If yes , date notified:	<input type="checkbox"/>	<input type="checkbox"/>		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>	Payment for this application (<i>check daily email from UserFeeAR@fda.hhs.gov:</i>) <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf	Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No			
505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment
Is the application a 505(b)(2) NDA? (<i>Check the 356h form, cover letter, and annotated labeling</i>). If yes , answer the bulleted	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

questions below:					
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		<input type="checkbox"/>	<input checked="" type="checkbox"/>		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].		<input type="checkbox"/>	<input checked="" type="checkbox"/>		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?		<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<p><i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i></p>					
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?		<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<p>Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p>					
If yes, please list below:					
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration		
<p><i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>					
Exclusivity	YES	NO	NA	Comment	
Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm	<input type="checkbox"/>	<input checked="" type="checkbox"/>			
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>					
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
<p>If yes, # years requested: 3</p>					
<p>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</p>					

NDA only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance? ¹ If not, explain (e.g., waiver granted).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Index: Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including: <input checked="" type="checkbox"/> legible	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				

Debarment Certification	YES	NO	NA	Comment
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829.htm>

<i>pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>				
If the application triggers PREA , is there an agreed Initial Pediatric Study Plan (iPSP)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, may be an RTF issue - contact DPMH for advice.</i>				
If required by the agreed iPSP , are the pediatric studies outlined in the agreed iPSP completed and included in the application?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, may be an RTF issue - contact DPMH for advice.</i>				
<u>BPCA:</u>				
Is this submission a complete response to a pediatric Written Request?	<input type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>				
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>				
REMS	YES	NO	NA	Comment
Is a REMS submitted?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>				
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If no, request applicant to submit SPL before the filing date.</i>				

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm>

Is the PI submitted in PLR format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
All labeling/packaging sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Meeting Minutes/SPAs	YES	NO	NA	Comment

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

End-of Phase 2 meeting(s)? Date(s): 9/9/13 <i>If yes, distribute minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): <i>If yes, distribute minutes before filing meeting</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

ATTACHMENT

MEMO OF FILING MEETING

DATE: April 13, 2015

BACKGROUND: Otonomy, Inc. has submitted a new drug application under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Ciprofloxacin (6% ciprofloxacin (b)(4) otic suspension), 60 mg/mL with the following indication: treatment of middle ear effusion in pediatric patients with otitis media undergoing tympanostomy tube placement.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Dean, Jane	Y
	CPMS/TL:		
Cross-Discipline Team Leader (CDTL)	Smith, Thomas		Y
Division Director/Deputy	Nambiar, Sumathi		Y
Office Director/Deputy			
Clinical	Reviewer:	Needles, Mark	Y
	TL:	Smith, Thomas	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	Sheikh, Jalal	Y
	TL:	Snow, Kerry	Y
Clinical Pharmacology	Reviewer:	Chilukuri, Dakshina	Y
	TL:	Bergman, Kimberly	Y
Biostatistics	Reviewer:	Rashid, Mushfiqur	Y
	TL:	Valappil, Thamban	Y

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Schmidt, Wendelyn	Y
	TL:	Wild, James	Y
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:		
Immunogenicity (assay/assay validation) (for protein/peptide products only)	Reviewer:	N/A	
	TL:		
Product Quality (CMC)	Reviewer:	Zhang , Chunchun	N
	TL:	Shanmugam, Balajee	Y
Biopharmaceutics	Reviewer	Zolnik, Banu	Y
	TL:		
Quality Microbiology	Reviewer:	Palmer-Ochien, Dupeh	N
	TL:		
CMC Labeling Review	Reviewer:	Zhang, Chunchun	N
	TL:		
Facility Review/Inspection	Reviewer:	Ramanadham, Mahesh	N
	TL:		
OSE/DMEPA (proprietary name, carton/container labels))	Reviewer:	Kolejian, Sevan	N
	TL:	Borders-Hemphill, Vicky	N
OSE/DRISK (REMS)	Reviewer:	Weaver, Joyce	
	TL:	Redd, Naomi	
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:		
Other reviewers/disciplines:	DPV Reviewer:	Jancel, Tim	
	DPV TL	Cao, Kelly	
	DEPI Reviewer:	Chen, Chih-Ying	
	DEPI TL:	Maloney, Elilizabeth	
Other attendees			

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> 505(b)(2) filing issues: <ul style="list-style-type: none"> Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., BA/BE studies):</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p>
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> No comments</p>
<p>CLINICAL</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> FILE</p> <p><input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>

<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CONTROLLED SUBSTANCE STAFF</p> <ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
IMMUNOGENICITY (protein/peptide products only) Comments:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
PRODUCT QUALITY (CMC) Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
New Molecular Entity (NDAs only) <ul style="list-style-type: none"> Is the product an NME? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<u>Environmental Assessment</u> <ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? If no, was a complete EA submitted? If EA submitted, consulted to EA officer (OPS)? Comments:	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<u>Quality Microbiology</u> <ul style="list-style-type: none"> Was the Microbiology Team consulted for validation of sterilization? Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> Establishment(s) ready for inspection? Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>CMC Labeling Review</u></p> <p>Comments: No review issues for 74-day letter.</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? If so, were the late submission components all submitted within 30 days? 	<p><input checked="" type="checkbox"/> N/A</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> What late submission components, if any, arrived after 30 days? 	
<ul style="list-style-type: none"> Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>

<ul style="list-style-type: none"> Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Sumathi Nambiar, MD, MPH, Director Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): 21st Century Review Milestones (see attached) (listing review milestones in this document is optional): Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, orphan drug).
<input type="checkbox"/>	If RTF, notify everyone who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	351(k) BLA/supplement: If filed, send filing notification letter on day 60
<input type="checkbox"/>	If priority review:

	<ul style="list-style-type: none"> • notify sponsor in writing by day 60 (see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for applications in the Program)
<input type="checkbox"/>	Other

Annual review of template by OND ADRA's completed: September 2014

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
05/18/2015

REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 207986

Application Type: New NDA

Name of Drug/Dosage Form: Ciprofloxacin (6% ciprofloxacin (b) (4) otic suspension), 60 mg/mL

Applicant: Otonomy, Inc.

Receipt Date: February 25, 2015

Goal Date: December 25, 2015

1. Regulatory History and Applicant's Main Proposals

Otonomy, Inc. has submitted a new drug application under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Ciprofloxacin (6% ciprofloxacin (b) (4) otic suspension), 60 mg/mL with the following indication: treatment of middle ear effusion in pediatric patients with otitis media undergoing tympanostomy tube placement.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by May 29, 2015. The resubmitted PI will be used for further labeling review.

Selected Requirements of Prescribing Information

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

- YES** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

Comment:

- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

- NO** 5. 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.

Comment: White space missing before several major headings: "Product Title, Indications and Usage, Dosage and Administration, Contraindications, Warnings and Precautions, and Drug Interactions".

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

- NO** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required

Selected Requirements of Prescribing Information

• 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.

Comment: Required "Patient Counseling Information" section heading is missing from Highlights

HIGHLIGHTS DETAILS

Highlights Heading

- YES 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

- YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: **"These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product)."** The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

- YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

- NO 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement **"Initial U.S. Approval:"** followed by the **4-digit year**.

Comment: Year 2016 incorrect if approved.

Boxed Warning (BW) in Highlights

- N/A 12. All text in the BW must be **bolded**.

Comment:

- N/A 13. The BW must have a heading in UPPER CASE, containing the word **"WARNING"** (even if more than one warning, the term, **"WARNING"** and not **"WARNINGS"** should be used) and

Selected Requirements of Prescribing Information

other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

Comment:

- N/A 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

- N/A 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).

Comment:

Recent Major Changes (RMC) in Highlights

- N/A 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

- N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

Comment:

- N/A 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

- NO 19. 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)”.

Comment: Missing the name of the established pharmacologic class. It should read as follows: “(Product) is a fluoroquinolone antibacterial indicated for . . .”

Dosage Forms and Strengths in Highlights

- N/A 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

Selected Requirements of Prescribing Information

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

- NO** 22. 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**”.

Comment: Delete the bolded title "Adverse Reaction Contact Information" preceding the above bolded verbatim statement under the Adverse Reactions heading in the Highlights section.

Patient Counseling Information Statement in Highlights

- NO** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

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

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

Revision Date in Highlights

- YES** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment:

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.
Comment:
- YES** 26. The following heading must appear at the beginning of the TOC: **“FULL PRESCRIBING INFORMATION: CONTENTS”**. This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- N/A** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- NO** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment: Section headings are not bolded.
- NO** 29. 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)].
Comment: Subsections are not indented.
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- NO** 31. 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.”
Comment: Unbold this statement: “*Sections or subsections omitted from the full prescribing information are not listed.”

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- NO** 32. 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

Comment: 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 on how to develop this section. Please submit a proposed Section 17.

- NO** 33. 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

Selected Requirements of Prescribing Information

within brackets. For example, “[see Warnings and Precautions (5.2)]” or “[see Warnings and Precautions (5.2)]”.

Comment: 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.

- N/A 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- NO 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

Comment: Font is only 8; it should be consistent with the font size of the other headings in the FPI.

BOXED WARNING Section in the FPI

- N/A 36. In the BW, all text should be **bolded**.

Comment:

- N/A 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

Comment:

CONTRAINDICATIONS Section in the FPI

- N/A 38. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- NO 39. 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.”

Comment: The above statement or appropriate modification was not included.

- N/A 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

Selected Requirements of Prescribing Information

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

- N/A 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment: *Patient counseling information missing.*

- N/A 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Additional Comment for Full Prescribing Information section:

We note that you included “Directions for Use” in section 16 (HOW SUPPLIED/STORAGE AND HANDLING) instead of section 2 (DOSAGE AND ADMINISTRATION).

According to 21 CFR 201.57 (c)(3) specific directions for administration of the dosage form must be included in Section 2 (DOSAGE AND ADMINISTRATION). Move the “Directions for Use” currently included 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.

Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

[section (X.X)] [m/year]
[section (X.X)] [m/year]

INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

[text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 [text]

2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 [text]

5.2 [text]

6 ADVERSE REACTIONS

6.1 [text]

6.2 [text]

7 DRUG INTERACTIONS

7.1 [text]

7.2 [text]

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

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 [text]

14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

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/s/

JANE A DEAN
04/28/2015