

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205433Orig1s000**

**OTHER REVIEW(S)**

### 505(b)(2) ASSESSMENT

Application Information		
NDA # 205433	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Kitabis Pak Established/Proper Name: Tobramycin Inhalation Solution (300 mg/vial), USP and PARI LC Plus Reusable Nebulizer Dosage Form: Inhalation Solution Strengths: 300 mg/vial		
Applicant: Pulmoflow, Inc. c/o Lachman Consultant Service, Inc.		
Date of Receipt: October 23, 2013 - (RS Class 1 October 2, 2014)		
PDUFA Goal Date: August 23, 2014 (TA action 08-22-14)	Action Goal Date (if different): 12-02-14	
RPM: Frances V. LeSane		
Proposed Indication(s): For the management of cystic fibrosis patients with <i>P. aeruginosa</i>		

### 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.*

**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)
<b>NDA 50753 TOBI (Tobramycin) Solution for Inhalation</b>	<b>FDA's previous finding of safety and effectiveness (e.g., clinical or nonclinical or both)</b>

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

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

**The proposed drug product, Tobramycin Inhalation Solution (300 mg/5mL) has undergone physic-chemical characterization in order to support the comparability with the references product TOBI. The drug product formulations are the same.**

**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

**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)
TOBI (Tobramycin Inhalation Solution)	NDA 50753	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 X

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 X

*(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”).

**Tobramycin Inhalation Solution (300 mg/vial) will be co-packaged with the approved 510(k) device PARI LC Plus Reusable Nebulizer.**

*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

**The drug is the same as the RLD but the product contains a device.**

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 X NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?  
N/A  YES X 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 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 X 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 X NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?  
N/A  YES X 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): NDAs 50519, 50541, 50616, 50555, 50592, 201688, 201820 and multiple generics are approved.

#### 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):**

**Patent Number: 5508269**

**Patent Expiration: October 19, 2014**

**\*\*Pulmoflow does not intend to market its proposed product until/after this patent expires. \*\***

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 X NO

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

- 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):

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

**Patent number(s): 5508269**

**Expiry date(s): October 19, 2014**

**\*\*Pulmoflow does not intend to market its proposed product until/after this patent expires.  
\*\***

- 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/  
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FRANCES V LESANE  
12/03/2014

**Division of Anti-Infective Drug Products**  
**REGULATORY PROJECT MANAGER LABELING REVIEW**

**Application:** NDA 205433

**Name of Drug:** Kitabis Pak Tobramycin Inhalation Solution (300 mg/vial), USP and PARI LC Plus Reusable Nebulizer

**Applicant:** Pulmoflow, Inc. c/o Lachman Consultant Service, Inc.

**Labeling Reviewed**

**Submission Date:** November 20, 2014

**Receipt Date:** November 20, 2014 and August 21, 2014

**Background and Summary Description:**

NDA 205433) Kitabis Pak Tobramycin Inhalation Solution (300 mg/vial), USP and PARI LC Plus Reusable Nebulizer is a 505(b)(2) application submitted October 2, 2013, received October 23, 2013.

The patent to the RLD (NDA 50-753) did not expire until October 19, 2014; therefore a tentative approval (TA) letter was issued on August 22, 2014. The sponsor submitted final draft labeling on August 21, 2014.

The NDA was resubmitted on October 2, 2014 (Class 1 resubmission); the goal date is December 2, 2014. A request for revisions to the label was sent to the sponsor on November 17, 2014. The Sponsor submitted a revised final label with the requested changes for the text for the package insert, text for the patient package insert, patient information, and PARI LC PLUS Reusable Nebulizer on November 20, 2014. These following changes will be included at the next printing of the label in February 2015.

**Kitabis Pak PI Label:**

[REDACTED] (b) (4)

**PARI LC PLUS Reusable Nebulizer label** revisions were made to the **Indication For Use, Safety Precautions, B- PARI LC PLUS Setup #4 and #9.**



**Review**

This review compares the final printed label submitted on November 20, 2014 with the tentative approval label on August 21, 2014. All changes were made as requested in the November 20, 2014 labeling.

**Recommendations**

An approval letter should be issued for NDA 205433 based on the final printed labeling submitted November 20, 2014.

Frances V. LeSane  
Chief, Regulatory Project Management Staff

11-22-14  
Date

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/s/  
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FRANCES V LESANE  
12/02/2014



Food and Drug Administration  
Anesthesia and Respiratory Devices Branch  
Division of Anesthesiology, General Hospital, Infection Control and Dental Device  
Office of Device Evaluation  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

**NDA 205433 – Regulatory Device Consult**

**Date:** August 20, 2014  
**To:** Frances V LeSane, Supervisory Consumer Safety Officer (OND IV/OAP/DAIP)  
**From:** James Lee Ph.D., Biomedical Engineer (ODE/DAGRID/RPDB), Lead Reviewer  
**Through:** Anya Harry, MD PhD, Branch Chief, RPDB  
CAPT Tejashri Purohit-Sheth MD, Clinical Deputy Director, DAGRID  
**Applicant:** Pari Respiratory Equipment, Inc.  
**Product Name:** KITABIS (tobramycin inhalation solution 300 mg/5 mL - and PARI LC® Plus Nebulizer)  
**Indication:** Tobramycin Inhalation Solution is indicated for the management of cystic fibrosis patients with P. aeruginosa.

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**A. Executive Summary:**

**Currently Proposed: NDA 205433**

Drug: KITABIS (Equivalent to Tobramycin Inhalation Solution (300 mg/5mL)  
Device: Pari LC® Plus  
Compressor: DeVilbiss Pulmo-Aide

**Originally Approved: NDA 050753**

Drug: Tobramycin Solution (300 mg/5mL)  
Device: Pari LC® Plus  
Compressor: DeVilbiss Pulmo-Aide

**Summary**

CDRH has been consulted on a combination product review for KITABIS (Equivalent to Tobramycin Inhalation Solution (300 mg/5mL) with a device component called Pari LC® Plus. Previously CDRH reviewed a draft protocol provided by the sponsor, Pari Respiratory Equipment, Inc which was addressed in Intercenter Consultation (ICC) provided to CDER/ ODE IV/OAP/DAIP regarding this Pre-IND 115904.

The sponsor has submitted protocols and bench tests to serve as a comparison between the proposed combination product and the original approved TOBI (Novartis, Switzerland). In the June 2013 the proposed protocol used multiple batches and multiple runs over each drug/device set. The protocol calls for the measurement of unit doses for weight of content, Tobramycin concentration, Tobramycin content. In terms of particle size distribution (PSD) the sponsor measured total dose, fine particle dose (b) (4) MMAD, GSD and Nebulizing time. Finally, the sponsor addressed and recorded the delivered dose characteristic. The protocol provided by the sponsor is adequate in bench testing the device performance

between the proposed product and the product in the originally approved NDA.

**B. Background:**

PARI Respiratory Equipment, Inc. wishes to pursue the approval of a marketing application for a combination product consisting of a drug and a cleared-to-market 510(k) device through the 505(b)(2) NDA process.

From the submission:

*PARI has developed a generic tobramycin inhalation solution (proposed name: KITABIS) to the reference listed product Novartis' Tobramycin Inhalation Solution TOBI (300 mg/5 mL), intended for (b)(4) management of chronic pulmonary infection due to Pseudomonas aeruginosa in cystic fibrosis (CF) patients aged 6 years and older. PARI is planning to submit a 505B(2) to CDER, Division of Anti-Infective products, applying for NDA in the US.*

In addition, the sponsor has provided a proposed *in vitro* test comparison between the 2 products.

*It is proposed to compare TEST and REF for Unit Dose Content (UDC), Particle Size Distribution (PSD) by Next Generation Impactor (NGI), and Delivered Dose (DD). PSD by (b)(4) is not considered required as PSD by NGI should provide sufficient information, in particular as solutions are studied.*

*Material For both KITABIS and TOBI, three different batches of formulation will be studied. Further, three different batches of PARI LC® Plus nebulizers (6 nebulizer units per batch), and three different units of the DeVilbiss compressor will be used. Testing for PSD and DD will be designed so all 6 formulation batches are tested using the same nebulizer unit and compressor unit in a balanced manner; see Table 2 for details.*

*Unit Dose Content*

*For each of the 6 batches, 10 vials will be assessed. For each the weight of content, concentration of tobramycin, and tobramycin content will be determined as per validated PARI in-house test method . Testing will be performed according to validated PARI in-house test method and equally divided between two analysts according to the design in Table 1.*

Regarding the original Pre-IND application sent in September 2012 including the 505b2 application with the novel drug being NDA 050753, TOBI® (Tobramycin Inhalation Solution, USP) 300 mg per 5 mL by Novartis Pharmaceuticals. Currently TOBI has been approved for administration by Pari LC® Plus and a DeVilbiss Pulmo-Aide air compressor. In PIND 115904, Pari Respiratory Equipment has proposed a formulation of inhaled Tobramycin Inhalation Solution, USP, paired with a cleared device the Pari LC® Plus reusable nebulizer. The submission intends to market a kit, where the drug and device would be marketed as the (b)(4) The proposed kit would contain 56 vials of Tobramycin Inhalation Solution, USP, 300mg/5mL, and one PARI LC® Plus Reusable  
6 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

**F. Labeling**

The sponsor has appropriately addressed the labeling performance of the device by providing statements that the PARI LC PLUS® Reusable Nebulizer has the following performance characteristics with Tobramycin Inhalation Solution [measured using Next Generation Impactor (NGI) at 15L/min continuous flow, standard conditions (50%RH, 23°C)]: (1) Delivered Dose: 174 mg; (2) Fine Particle Dose (<5µm): 97 mg; (3) Nebulization Time: 13 min.; (4) Mass Median Aerodynamic Diameter: 4.3 µm; (5) Geometric Standard Deviation (GSD): 2.2 µm.

The device instructions for use are nearly identical to other nebulizers and are appropriate for this combination product.

**G. Recommendation**

The sponsor has provided appropriate information regarding the device performance to show that the device component of this combination product performs in statistically similar fashion to the subject of the 505b2. The performance and safety information of the device is supportive of device use with the proposed drug.

<b>Digital Signature Concurrence Table</b>	
Reviewer Sign-Off	
Branch Chief Sign-Off	
Division Sign-Off	

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/s/  
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FRANCES V LESANE  
08/21/2014

## 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 # 205433 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Kitabis Pak Established/Proper Name: Tobramycin Inhalation Solution and LC Plus Nebulizer Dosage Form: Inhalation Strengths: 300 mg/vial		
Applicant: PulmoFlow , Inc. Agent for Applicant (if applicable): Lachman Consultant Services, Inc.		
Date of Application: 10-2-13 Date of Receipt: 10-23-13 Date clock started after UN: 10-23-13		
PDUFA Goal Date: August 23, 2014		Action Goal Date (if different): N/A
Filing Date: January 5, 2014		Date of Filing Meeting: December 12, 2013
Chemical Classification: (1, 2,3 etc.) (original NDAs only) 5S		
Proposed indication(s)/Proposed change(s): For the management of cystic fibrosis patients with <i>P. aeruginosa</i> .		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a> and refer to Appendix A for further information.</i>	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
Review Classification:  <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>  <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority  <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? X  <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 <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 [21 CFR 314.55(b)/21 CFR 601.27(b)] <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): N/A				
List referenced IND Number(s): N/A				
<b>Goal Dates/Product Names/Classification Properties</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
PDUFA 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>	X	<input type="checkbox"/>		
Are the proprietary, 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 system.</i>	X	<input type="checkbox"/>		
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</a></i>  <i>If no, ask the document room staff to make the appropriate entries.</i>	X	<input type="checkbox"/>	<input type="checkbox"/>	Standard 505(b)(2)
<b>Application Integrity Policy</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></i>	<input type="checkbox"/>	X		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:</i>	<input type="checkbox"/>	<input type="checkbox"/>		
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X	<input type="checkbox"/>		

<p><u>User Fee Status</u></p> <p><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></p>	<p>Payment for this application:</p> <p><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</p>																			
<p><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></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears  <input type="checkbox"/> In arrears</p>																			
<p><b>505(b)(2)</b>  <b>(NDAs/NDA Efficacy Supplements only)</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>	<p><input type="checkbox"/></p>																	
<p>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)].</p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>	<p><input type="checkbox"/></p>																	
<p>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)]?</p> <p><i>If you answered yes to any of the above 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</i></p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>	<p><input type="checkbox"/></p>																	
<p>Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</p> <p><i>Check the Electronic Orange Book at:</i>  <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a></p> <p><b>If yes, please list below:</b></p> <table border="1" data-bbox="203 1482 1349 1619"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration													<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>	<p><input type="checkbox"/></p>	
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, 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>																				
<p><b>Exclusivity</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug</i></p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>																		

<b>Designations and Approvals list at:</b> <a href="http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</a>				
<b>If another product has orphan exclusivity</b> , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?  <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>	<input type="checkbox"/>	<input type="checkbox"/>	X	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ( <i>NDAs/NDA efficacy supplements only</i> )  If yes, # years requested:  <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input type="checkbox"/>	X	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use ( <i>NDAs only</i> )?	<input type="checkbox"/>	X	<input type="checkbox"/>	
<b>If yes</b> , 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 Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

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

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

X legible X English (or translated into English) X pagination X navigable hyperlinks (electronic submissions only)				
<b>If no, explain.</b>				
<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?	<input type="checkbox"/>	<input type="checkbox"/>	X	
<b>If yes, BLA #</b>				
<b>Forms and Certifications</b>				
<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), 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>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X	<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?	X	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	<input type="checkbox"/>	X		No clinical studies conducted in support of this application
<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>				
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 3674 included with authorized signature?	<input type="checkbox"/>	X		No clinical studies
<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>				
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a correctly worded Debarment Certification included with authorized signature?  <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <b>both</b> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i>  <i>Note: Debarment Certification should use wording in FD&amp;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>	<input type="checkbox"/>	X	<input type="checkbox"/>	Will ask sponsor to submit
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?  <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>  <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	<input type="checkbox"/>	<input type="checkbox"/>	X	Electronic Submission
<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?  <i>If yes, date consult sent to the Controlled Substance Staff:</i>  <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>	<input type="checkbox"/>	<input type="checkbox"/>	X	
<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b><u>PREA</u></b> Does the application trigger PREA?  <i>If yes, notify PeRC RPM (PeRC meeting is required)<sup>2</sup></i>  <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be</i>	<input type="checkbox"/>	<input type="checkbox"/>		Criteria does not apply, exempt from requirements Sponsor request for a waiver.

<sup>2</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

<i>reviewed by PeRC prior to approval of the application/supplement.</i>				
<b>If the application triggers PREA</b> , are the required pediatric assessment studies or a full waiver of pediatric studies included?	<input type="checkbox"/>	<input type="checkbox"/>	X	
<b>If studies or full waiver not included</b> , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>	X	<input type="checkbox"/>	<input type="checkbox"/>	
<b>If a request for full waiver/partial waiver/deferral is included</b> , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>	<input type="checkbox"/>	<input type="checkbox"/>	X	
<b>BPCA (NDAs/NDA efficacy supplements only):</b>  Is this submission a complete response to a pediatric Written Request?  <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i>	<input type="checkbox"/>	X		
<b>Proprietary Name</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a proposed proprietary name submitted?  <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	X	<input type="checkbox"/>	<input type="checkbox"/>	
<b>REMS</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a REMS submitted?  <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input type="checkbox"/>	X	<input type="checkbox"/>	
<b>Prescription Labeling</b>	<input type="checkbox"/> <b>Not applicable</b>			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input checked="" 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)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL	<input type="checkbox"/>	X		Will ask sponsor to submit.

<sup>3</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

format?				
<i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in PLR format? <sup>4</sup>	<input type="checkbox"/>	X		Request in 74 day letter
<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?	<input type="checkbox"/>	X	<input type="checkbox"/>	Request in 74 day letter
<i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X	<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)?	X	<input type="checkbox"/>	<input type="checkbox"/>	
<b>OTC Labeling</b>	<b>X Not Applicable</b>			
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)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted?	<input type="checkbox"/>	<input type="checkbox"/>		
<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Other Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	X	<input type="checkbox"/>	<input type="checkbox"/>	11-26-13 12-04-13

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

<i>If yes, specify consult(s) and date(s) sent:</i>				
<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of Phase 2 meeting(s)? <b>Date(s):</b>	<input type="checkbox"/>	X		
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> September 27, 2012	X	<input type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b>	<input type="checkbox"/>	X		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** December 12, 2013

**BLA/NDA/Supp #:** NDA 205433

**PROPRIETARY NAME:** Kitabis

**ESTABLISHED/PROPER NAME:** Tobramycin Inhalation Solution, USP and PARI LC® Plus Reusable Nebulizer)

**DOSAGE FORM/STRENGTH:** 300 mg/vial

**APPLICANT:** Pulmoflow Inc. c/o Lachman Consultant Services, Inc.

**PROPOSED INDICATION(S)/PROPOSED CHANGE(S):** *For the management of cystic fibrosis patients with P. aeruginosa*

**BACKGROUND:** Pulmoflow Inc. c/o Lachman Consultant Services, Inc. submitted a 505(b)(2) application relying on the Reference Listed Drug (RLD) NDA 50753 TOBI (tobramycin inhalation solution) sponsor Novartis approved December 22, 1997.

**REVIEW TEAM:**

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Frances LeSane	Y
	CPMS/TL:	Same	
Cross-Discipline Team Leader (CDTL)			
Clinical	Reviewer:	Shrimant Mishra	Y
	TL:	Ben Lorenz	Y
Clinical Microbiology ( <i>for antimicrobial products</i> )	Reviewer:	Peter Coderre	Y
	TL:	Kerry Snow	Y

Clinical Pharmacology	Reviewer:	Ryan Owen	Y
	TL:	Kimberly Bergman	Y
Biostatistics	Reviewer:	Christopher Kadoorie	Y
	TL:	Thamban Valappil	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Amy Ellis	Y
	TL:	Wendelyn Schmidt	Y
Product Quality (CMC)	Reviewer:	Mark Seggel	Y
	TL:	Dorota Matecka	Y
Quality Microbiology ( <i>for sterile products</i> )	Reviewer:	Steven Donald	Y
	TL:	Bryan Riley	N
CMC Labeling Review	Reviewer:	N/A	
	TL:	N/A	
Facility Review/Inspection	Reviewer:	Steve Hertz	Y
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Karen Townsend	Y
Other reviewers – Biopharmaceutics	Reviewer:	Sandra Suarez	Y
Other attendees –	James J. Lee (CDRH) Patricia Love – Combination Products Bindi Nikhar– Combination Products Sumathi Nambiar Katherine Laessig John Farley	Y Y Y Y Y Y	

**FILING MEETING DISCUSSION:**

<p><b>GENERAL</b></p> <ul style="list-style-type: none"> <li>• 505(b)(2) filing issues: <ul style="list-style-type: none"> <li>○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</li> </ul> </li> </ul>	<input type="checkbox"/> Not Applicable  <input type="checkbox"/> YES X NO
--	--

<ul style="list-style-type: none"> <li>○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature?</li> </ul> <p>Describe the scientific bridge (e.g., BA/BE studies):</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO  Bio waiver requested
<ul style="list-style-type: none"> <li>• Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no</b>, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Electronic Submission comments</li> </ul> <p><b>List comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable
<p><b>CLINICAL</b></p> <p><b>Comments:</b></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"> <li>• Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no</b>, explain: No clinical studies conducted.</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></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"> <li>○ <i>this drug/biologic is not the first in its class</i></li> <li>○ <i>the clinical study design was acceptable</i></li> <li>○ <i>the application did not raise significant safety or efficacy issues</i></li> <li>○ <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></li> </ul>	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined  Reason: N/A
<ul style="list-style-type: none"> <li>• Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></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
<ul style="list-style-type: none"> <li>• If the application is affected by the AIP, has the division made a recommendation regarding whether</li> </ul>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES

<p>or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</p> <p><b>Comments:</b></p>	<input type="checkbox"/> NO
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></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><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b></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"> <li>Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>BIOSTATISTICS</b></p> <p><b>Comments:</b></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><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p> <p><b>Comments:</b></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><b>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</b></p> <p><b>Comments:</b></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><b>PRODUCT QUALITY (CMC)</b></p> <p><b>Comments:</b></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><b><u>Environmental Assessment</u></b></p> <ul style="list-style-type: none"> <li>Categorical exclusion for environmental assessment</li> </ul>	<input type="checkbox"/> YES

<p>(EA) requested?</p> <p><b>If no</b>, was a complete EA submitted?</p> <p><b>If EA submitted</b>, consulted to EA officer (OPS)?</p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><b><u>Quality Microbiology (for sterile products)</u></b></p> <ul style="list-style-type: none"> <li>Was the Microbiology Team consulted for validation of sterilization? (<b>NDAs/NDA supplements only</b>)</li> </ul> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable</p> <p>X YES <input type="checkbox"/> NO</p>
<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>Establishment(s) ready for inspection?</li> <li>Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ?</li> </ul> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable</p> <p>X YES <input type="checkbox"/> NO</p> <p>X YES <input type="checkbox"/> NO</p>
<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p><b>Comments:</b></p>	<p>X 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><b><u>CMC Labeling Review</u></b></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>

<b>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</b>		X N/A
<ul style="list-style-type: none"> <li>• 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?</li> </ul>	<input type="checkbox"/> YES <input type="checkbox"/> NO	
<ul style="list-style-type: none"> <li>• If so, were the late submission components all submitted within 30 days?</li> </ul>	<input type="checkbox"/> YES <input type="checkbox"/> NO	
<ul style="list-style-type: none"> <li>• What late submission components, if any, arrived after 30 days?</li> </ul>		
<ul style="list-style-type: none"> <li>• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?</li> </ul>	<input type="checkbox"/> YES <input type="checkbox"/> NO	
<ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?</li> </ul>	<input type="checkbox"/> YES <input type="checkbox"/> NO	
<ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?</li> </ul>	<input type="checkbox"/> YES <input type="checkbox"/> NO	
<b>REGULATORY PROJECT MANAGEMENT</b>		
<b>Signatory Authority:</b> Frances V. LeSane  <b>Date of Mid-Cycle Meeting</b> (for NME NDAs/BLAs in "the Program" PDUFA V):  <b>21<sup>st</sup> Century Review Milestones (see attached)</b> (listing review milestones in this document is optional):  <b>Comments:</b>		
<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>		
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:	
X	The application, on its face, appears to be suitable for filing.	

	<p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p>X Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p>X Standard Review</p> <p><input type="checkbox"/> Priority Review</p>
<b>ACTIONS ITEMS</b>	
<input 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, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody 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"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	<p>If priority review:</p> <ul style="list-style-type: none"> <li>• notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)</li> <li>• notify OMPQ (so facility inspections can be scheduled earlier)</li> </ul>
X	Send review issues/no review issues by day 74
<input 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 NME NDAs in the Program)
<input type="checkbox"/>	<p>BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at:</p> <p><a href="http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f">http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f</a>]</p>
<input type="checkbox"/>	Other

## Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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/s/  
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FRANCES V LESANE  
08/20/2014

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Medical Policy**

**PATIENT LABELING REVIEW**

Date: July 24, 2014

To: John Farley, MD, MPH  
Director  
**Division of Products Anti-Infective Products (DAIP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN  
Associate Director for Patient Labeling  
**Division of Medical Policy Programs (DMPP)**  
Melissa Hulett, MSBA, MSN, FNP-BC, RN  
Team Leader, Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

From: Shawna Hutchins, MPH, BSN, RN  
Senior Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**  
Christine Corser, PharmD, RAC  
Regulatory Review Officer  
**Office of Prescription Drug Promotion (OPDP)**

Subject: Review of Patient Labeling: Patient Package Insert (PPI) and  
Instructions for Use (IFU)

Drug Name (established name): KITABIS PAK (tobramycin inhalation solution)

Dosage Form and Route: for oral inhalation

Application Type/Number: NDA 205433

Applicant: Pulmoflow Inc.

## 1 INTRODUCTION

On October 02, 2013, Pulmoflow Inc., submitted for the Agency's review a New Drug Application (NDA-205433) for KITABIS PAK (tobramycin inhalation solution) an aminoglycoside antibacterial indicated for the management of cystic fibrosis in adults and children six years of age and older with pseudomonas aeruginosa. The purpose of the submission was to propose the co-packing of tobramycin inhalation solution with the PARI LC PLUS Reusable Nebulizer.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Anti-Infective Products (DAIP) on July 02, 2014, and March 4, 2014, respectively, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for KITABIS PAK (tobramycin inhalation solution).

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU was completed on June 24, 2014.

## 2 MATERIAL REVIEWED

- Draft KITABIS PAK (tobramycin inhalation solution) PPI and IFU received on July 21, 2014 and received by DMPP on July 22, 2014.
- Draft KITABIS PAK (tobramycin inhalation solution) PPI and IFU received on July 21, 2014 and received by OPDP on July 22, 2014.
- Draft KITABIS PAK (tobramycin inhalation solution) Prescribing Information (PI) received on October 02, 2013, revised by the Review Division throughout the review cycle, and received by DMPP on July 22, 2014.
- Draft KITABIS PAK (tobramycin inhalation solution) Prescribing Information (PI) received on October 02, 2013, revised by the Review Division throughout the review cycle, and received by OPDP on July 22, 2014.
- Approved BETHKIS (tobramycin inhalation solution) comparator labeling dated October 12, 2012.

## 3 REVIEW METHODS

In 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI and IFU document using the Verdana font, size 11.

In our collaborative review of the PPI and IFU we have:

- simplified wording and clarified concepts where possible

- ensured that the PPI and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI and IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI and IFU are consistent with the approved comparator labeling where applicable
- The enclosed IFU review comments are collaborative DMPP and DMEPA.

#### **4 CONCLUSIONS**

The PPI and IFU are acceptable with our recommended changes.

#### **5 RECOMMENDATIONS**

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI and IFU are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.

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/s/  
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SHAWNA L HUTCHINS  
07/24/2014

CHRISTINE G CORSER  
07/25/2014

MELISSA I HULETT  
07/25/2014

LASHAWN M GRIFFITHS  
07/25/2014

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

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

## Memorandum

**Date:** July 16, 2014

**To:** Frances LeSane, Chief Project Management Staff  
Division of Anti-Infective Products (DAIP)

Shrimant Mishra, MD, MPH, Medical Officer  
DAIP

**From:** Christine Corser, PharmD, RAC, Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)

**Subject:** NDA #205433  
KITABIS PAK (tobramycin inhalation solution USP), for oral  
inhalation use - OPDP Labeling Comments

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As requested in your consult dated March 4, 2014, the Office of Prescription Drug Promotion (OPDP) has reviewed the draft labeling for KITABIS PAK (tobramycin inhalation solution USP), for oral inhalation use (Kitabis PAK).

OPDP's comments on the PI are based on the substantially complete clean WORD version of the labeling titled, "Substantially Complete Kitabis Pak Label.doc" which was received via email from DAIP on July 15, 2014. OPDP's comments are provided in the attached, clean version of the labeling.

If you have any questions, please contact Christine Corser at 6-2653 or at [Christine.Corser@fda.hhs.gov](mailto:Christine.Corser@fda.hhs.gov).

Thank you for the opportunity to provide comments on this PI.

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/s/  
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CHRISTINE G CORSER  
07/16/2014

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## **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\*\*\***

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**Date of This Review:** June 24, 2014

**Requesting Office or Division:** Division of Anti-Infective Products (DAIP)

**Application Type and Number:** NDA 205433

**Product Name and Strength:** Kitabis Pak (Tobramycin Inhalation Solution and Pari LC® Plus Reusable Nebulizer ), 300 mg/5 mL

**Product Type:** Co-Packaged Single Ingredient Product with Device

**Rx or OTC:** Rx

**Applicant/Sponsor Name:** Pulmoflow Inc.

**Submission Date:** September 26, 2013

**OSE RCM #:** 2013-2701

**DMEPA Primary Reviewer:** Aleksander Winiarski, PharmD

**DMEPA Acting Team Leader:** Tingting Gao, PharmD

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## 1 REASON FOR REVIEW

Pulmoflow developed a co-packaged product which includes Tobramycin Inhalation Solution 300 mg/5 mL and Pari LC® Plus Reusable Nebulizer under NDA 205433. This is a 505(b)(2) application and the Applicant referred the listed drug, TOBI (Tobramycin Inhalation Solution) for 300 mg/5 mL, NDA 050753.

The Division of Anti-Infective Products (DAIP) requested that we review the submitted Kitabis Pak container labels and carton and prescribing information 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.

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

N/A = Not applicable for this review

## 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We identified three new medication error cases in the FAERS database that may be relevant to the submitted labels or labeling (See Appendix B2). One case described an overdose by a patient who used 4 ampules instead of 1 ampule for the dose. The remaining two cases described wrong frequency of administration (e.g. once daily instead of twice daily). In all three cases, the root cause of the errors could not be determined from the limited information provided.

We evaluated the submitted prescribing information (PI) labeling and identified that the PI clearly states that the administration frequency is twice daily (we recommend changing the abbreviation BID to twice daily in the Dosage and Administration section of the submitted PI) and that the dose is 300 mg or 1 ampule. Therefore, we conclude that the submitted PI labeling is adequate to minimize the risk for these errors. However, although the PI and carton/ pouch labeling is clear, the packaging configuration (4 LDPE ampules per pouch) may contribute to the occurrence of overdose errors. In this review, we identified a second case (first case identified in OSE #2010-2309) that describes a patient who received the contents of 1 foil pack (4 LDPE ampules) instead of 1 ampule, resulting in a 4 fold overdose and adverse reactions. This medication error will be discussed further with the Review Division to determine if the Agency can recommend any additional mitigation strategies beyond labeling.

We note that in the submission that Pulmoflow refers to the product as “Tobramycin Inhalation Solution, USP and PARI LC® Plus Reusable Nebulizer”. In addition, the established name on the submitted outer carton labeling only refers to the Tobramycin Inhalation Solution. Therefore, we brought this issue to the attention of our Office of New Drugs Quality Assessment (ONDQA) colleagues to determine the correct established name to be listed on the outer carton for the Kitabis Pak.

Additionally, in our review of the submitted labels and labeling, we identified lack of prominence of important use/prescribing information, and the use of abbreviations such as “BID” in the PI, which should be replaced with the corresponding words for clarity. We provide specific recommendations in sections 4.1 and 4.2 below.

## **4 CONCLUSION & RECOMMENDATIONS**

The submitted container labels and carton and prescribing information labeling for Kitabis Pak may be improved to communicate important use information and to improve prominence of product information. We recommend the following revisions be implemented prior to the approval of this NDA.

### **4.1 RECOMMENDATIONS FOR THE DIVISION**

DMEPA provides the following comments for the Division’s consideration

#### **A. Dosage and Administration Sections, Highlights of Prescribing Information and Full Prescribing Information**

1. We note the use of the “BID” abbreviation, which may be misinterpreted, consider replacing the abbreviation “BID” with the corresponding words “twice daily or twice per day” for clarity.

## 4.2 RECOMMENDATIONS FOR PULMOFLOW

DMEPA recommends the following revisions prior to approval of the NDA:

### A. Outer Carton Labeling

1. Ensure that you revise the labeling with the currently conditionally approved proprietary name “Kitabis Pak”.
2. Ensure that the established name is at least half the size of the proprietary name per 21CFR 201.10(g)(2).
3. The graphic design located to the left of the proprietary name is prominent and may be misinterpreted as part of the proprietary name. On all panels, delete this graphic, or reduce the size of the graphic design and relocate it further away from the proprietary name.<sup>1</sup>
4. The net quantity statement “56 Single-Use Ampules (28-Day Supply)” competes for prominence with the strength “300 mg/5 mL” statement. On all panels, to improve the prominence of the strength, increase the size of the strength statement and relocate it further away from the net quantity statement, such as to directly below the established name. Also consider relocating the net quantity statement further away from the strength, such as to the bottom third of the panels (e.g. below the “for inhalation only by nebulizer and contains no preservatives” statements).
5. The Pari LC Plus logo, which also contains the nebulizer net quantity statement, competes for prominence with the most important prescribing information, such as the proprietary name, established name and strength statement. On all panels, delete this logo or significantly reduce the size of this logo (at least by half) and revise the net quantity statement to include the nebulizer. For example:

This Pak includes:

- 56 Single-Use Ampules (28-Day Supply)  
(14 foil pouches – each pouch contains 4 Single-Use Ampules)
- 1 reusable nebulizer

### B. Inner Carton Labeling

1. See A4 above.

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<sup>1</sup> 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>.

2. The Pari logo in the upper right corner of the principal display panel (PDP) competes for prominence with the most important prescribing information such as the established name and strength. On all panels, to ensure that the established name is the most prominent information on the inner carton, move the Pari logo to the bottom third of the PDP and significantly increase the font size of the established name.
3. Revise the net quantity statement to reflect the entire packaging configuration. For example:
  - 56 Single-Use Ampules (28-Day Supply)  
(14 foil pouches – each pouch contain 4 Single-Use Ampules)

### C. Foil Pouch Labeling



### D. Ampule label



## E. Nebulizer Carton

1. To ensure clarity of the intended use, consider adding a statement similar to: “For Use With Co-packaged Tobramycin Inhalation Solution Only” above the statement “Not For Resale”.

## APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

### APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Kitabis Pak from the submitted insert labeling on October 2, 2013.

Table 2. Relevant Product Information for Kitabis Pak	
Active Ingredient	Tobramycin
Indication	Management of cystic fibrosis patients with <i>P. aeruginosa</i> .
Route of Administration	Oral inhalation via nebulizer
Dosage Form	Co-packaged Inhalation Solution and Nebulizer
Strengths	300 mg per 5 mL
Dose and Frequency	1 ampule or 300 mg twice daily
How Supplied	Carton of 56 ampules and 1 reusable nebulizer
Storage	Refrigerated temperature
Container Closure	4 LDPE ampules packed in individual foil pouch then in inner carton and outer carton. The nebulizer is also packed in one inner carton.

### APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

#### B.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on June 17, 2014 using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the labels and labeling. We used the NCC MERP

Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter<sup>2</sup>

<b>Table 3: FAERS Search Strategy</b>	
<b>Search Date</b>	<b>April 25, 2011* to June 17, 2014</b> *Date of last FAERS search in previous relevant OSE review # 2010-2309
<b>Drug Names</b>	Tobi [product name]
<b>MedDRA Search Strategy</b>	<b>Medication Errors [HLGT]</b> <b>Product Packaging Issues [HLT]</b> <b>Product Label Issues [HLT]</b> <b>Product Quality Issues (NEC)[HLT]</b>

## B.2 Results

Our search identified 52 reports, of which 3 described an error that may be relevant to the submitted labels and labeling for Kitabis Pak, NDA 205433. We excluded 49 cases because they describe:

- Off label use
  - use in pediatrics younger than 6 years old (n=29)
  - use to treat for bronchiectasis (n=4)
  - use to treat chronic airway obstruction (n=1)
  - use to treat pseudomonas pneumonia in tracheotomy patient (n=1)
- Adverse reaction unrelated to a medication error (n=3)
- No medication error occurred
  - Cystic fibrosis flare up/ pulmonary exacerbation/additional infections (n=3)
  - Mention of incomplete use, possible device malfunction but cause unclear (n=1)
- Non-compliance to prescribed dosage regimen (n=2)
- Case related to an intravenous dosage form of Tobramycin (n=1)
- Reference made to wrong dosage form of Tobramycin (“e.g. taken Tobi in IV form or TOBI IV”) (n=2)

<sup>2</sup> The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>.

- Unintentional exposure by nurse administering the nebulizer (n=1)
- Wrong technique in the use process - patient used different nebulizer than recommended (root cause unclear), this case is not relevant to the submitted NDA 205433 because the drug and nebulizer is co-packaged, however we recommend adding a statement on the carton of the nebulizer that it is for use with the co-packaged Tobramycin inhalation solution only for clarity.

Following exclusion, we further analyzed the remaining 3 cases because they may be relevant to the submitted labels and labeling for Kitabis Pak.

#### Overdose (n = 1) Case number 8476980

One case described a patient who received a prescription for TOBI 300 mg/5 mL once daily for bronchiectasis (off-label use). However, the case reported that the patient took 4 doses, the cause was describe in the case as “they were purchased together and pharmacy instructions were not clear”. The error was identified the following day (“UNA” unclear by whom) and the patient was instructed about proper use. The patient developed worsening hearing impairment which eventually resolved. It’s unclear from the limited information in the case if the overdose error was related to the pharmacy label and/or if it was related to the packaging design because each single foil pouch contains 4 ampules that are joined together. We plan to continue monitoring this potential error because the Tobramycin Inhalation Solution under NDA 205433 is packed in the same configuration as the Tobi.

#### Wrong frequency (n = 2) Case numbers 9688043 and 9835599

Two cases were identified which describe wrong frequency of administration. Both cases describe patients who received Tobi once daily for the treatment of Cystic Fibrosis (indicated frequency is twice daily).

- In the first case the 82 year old female patient died on an unknown date, the cause of death was not determined and there was no additional information provided.
- In the second case the 46 year old female patient initially received Tobi twice daily and then, on an unknown date, received Tobi once daily. The patient was noted to have renal failure while therapy with Tobi was ongoing, therefore dose adjustment may have been appropriate if serum Tobramycin levels were being monitored, however that information was not provided. There were not outcomes specified related to the once daily regimen.

In both cases, the root cause of the errors could not be determined from the limited information provided.

We evaluated the submitted Kitabis Pak prescribing information (PI) labeling and identified that the PI clearly states that the administration frequency is twice daily and that the dose is 300 mg per 5 mL or 1 ampule. Therefore, we conclude that the submitted PI labeling is adequate to

minimize the risk for these errors. However we will discuss the overdose error further with the Review Division to determine if the Agency can recommend any additional mitigation strategies beyond labeling.

### B.3 List of FAERS Case Numbers, Submitted Narratives, and Assessment of Cases

Below is a list of the FAERS case number and manufacturer control numbers for the cases relevant for this review.

Case #	Vrsn	MFR Ctrl #	Country
<a href="#">8476980</a>	2	PHEH2012US006507	USA
<a href="#">9688043</a>	1	PHEH2013US023785	USA
<a href="#">9835599</a>	1	PHEH2014US001437	USA

### B.4 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>.

## APPENDIX C. PREVIOUS DMEPA REVIEWS

### C.1 Methods

We searched the L:drive on June 17, 2014 using the terms Tobramycin and Tobi to identify reviews previously performed by DMEPA.

### C.2 Results

We identified one relevant review, OSE# 2010-2309.

The review described 10 relevant cases of medication errors for TOBI (tobramycin inhalation solution). Four cases described wrong drug administered due to similarity of low-density polyethylene (LDPE) packaging between inhalation solutions, which is a well know issue. Two cases described underdose, and single cases described wrong nebulizer used, wrong frequency of administration, wrong duration of administration, and overdose (4 ampules or 1200 mg). None of the cases attributed the root causes to the labels or labeling.

## APPENDIX E. ISMP NEWSLETTERS

### E.1 Methods

We searched the Institute for Safe Medication Practices (ISMP) newsletters on June 17, 2014 using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care, Community/Ambulatory Care
Search Strategy and Terms	Match Any of the words: Tobi, Tobramycin inhalation, Tobramycin nebulized

### E.2 Results

Our search did not identify any relevant articles.

## APPENDIX G. LABELS AND LABELING

### G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>2</sup> along with postmarket medication error data, we reviewed the following Kitabis Pak labels and labeling submitted by Pulmoflow on October 2, 2013 and June 11, 2014.

### G.2 Label and Labeling Images

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<sup>2</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/  
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ALEKSANDER P WINIARSKI  
06/24/2014

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06/24/2014