

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205433Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 205433

SUPPL #

HFD #

Trade Name Kitabis Pak PARI LC PLUS Reusable Nebulizer

Generic Name Tobramycin Inhalation Solution

Applicant Name Pulmoflow Inc. c/o Lachman Consultant Services, Inc.

Approval Date, If Known December 2, 2014

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(2)

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

YES ☐ NO ☒

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

N/A

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

d) Did the applicant request exclusivity?

YES ☐ NO ☒

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

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

YES ☐ NO ☒

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

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

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

YES ☐ NO ☒

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES ☒ NO ☐

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

NDA# 50-753	TOBI (tobramycin) Solution for Inhalation 300 mg
NDA# 50-789	Tobramycin Injection
NDA# 201820	Bethkis (tobramycin 300mg/4mL) Inhalation Solution

2. Combination product.

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

YES ☐ NO ☒

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

NDA#

NDA#

NDA#

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

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical

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

YES ☐ NO ☒

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

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

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

YES ☐ NO ☐

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

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

YES ☐ NO ☐

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

YES ☐ NO ☐

If yes, explain:

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

YES ☐ NO ☐

If yes, explain:

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

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

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

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

YES ☐ NO ☐

YES ☐ NO ☐

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

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

YES ☐ NO ☐
YES ☐ NO ☐

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

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

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

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

YES ☐ ! NO ☐
! Explain:

!
IND # YES ☐ ! NO ☐
! Explain:

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

Investigation #1 !

YES ☐

Explain:

!

! NO ☐

! Explain:

Investigation #2

!

!

YES ☐

Explain:

! NO ☐

! Explain:

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

YES ☐

NO ☐

If yes, explain:

Name of person completing form: Frances V. LeSane

Title: Chief, Regulatory Project Management Staff

Date: November 24, 2014

Name of Office/Division Director signing form: Katherine A. Laessig, MD

Title: Deputy Director

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

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

/s/

FRANCES V LESANE
12/01/2014

KATHERINE A LAESSIG
12/02/2014

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 205433 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Kitabis Pak Established/Proper Name: Tobramycin Inhalation Solution, USP and PARI LC Plus Reusable Nebulizer Dosage Form: 300 mg/5mL ampule		Applicant: PulmoFlow Inc. Agent for Applicant (if applicable): Donald Chmielewski/Lachman Consultant Services, Inc.
RPM: Frances V. LeSane		Division: Anti-Infective Products
NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) BLA Application Type: ☐ 351(k) ☐ 351(a) Efficacy Supplement: ☐ 351(k) ☐ 351(a)		<u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u> - Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. - Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) ☒ No changes ☐ New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check: November 24, 2014 <i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i>
❖ Actions		
- Proposed action - User Fee Goal Date is December 2, 2014		☒ AP ☐ TA ☐ CR
Previous actions <i>(specify type and date for each action taken)</i>		☐ None TA 08-22-14
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		☐ Received – N/A
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): 5S
(confirm chemical classification at time of approval)

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

NDAs: Subpart H

- ☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)

Subpart I

- ☐ Approval based on animal studies

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

BLAs: Subpart E

- ☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)

Subpart H

- ☐ Approval based on animal studies

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

Comments:

❖ BLAs only: Ensure RMS-BLA Product Information Sheet for TBP and RMS-BLA Facility Information Sheet for TBP have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)	☐ Yes ☐ No
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Indicate what types (if any) of information were issued	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only)	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters <i>(including approval letter with final labeling)</i>	Action(s) and date(s) AP – December 2, 2014 Tentative Approval August 22, 2014
Labeling	
❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	
• Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i>	X ☐ Included 11-20-14 (Final)
• Original applicant-proposed labeling	X ☐ Included 10-2-13
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling <i>(write submission/communication date at upper right of first page of each piece)</i>	☐ Medication Guide X ☐ Patient Package Insert X ☐ Instructions for Use X ☐ Device Labeling ☐ None
• Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i>	☐
• Original applicant-proposed labeling	☐
❖ Labels (full color carton and immediate-container labels) <i>(write submission/communication date on upper right of first page of each submission)</i>	
• Most-recent draft labeling	X ☐ Included 7-18-14
❖ Proprietary Name	
• Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i>	Acceptable June 2, 2014
• Review(s) <i>(indicate date(s))</i>	Review June 2, 2014
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: X ☐ 12-1-14 DMEPA: X ☐ June 24, 2014 DMPP/PLT (DRISK): X 7-24-14 OPDP: ☐ July 16, 2014 SEALD: ☐ None CSS: ☐ None Other: ☐ None
Administrative / Regulatory Documents	
❖ Administrative Reviews <i>(e.g., RPM Filing Review⁴/Memo of Filing Meeting) (indicate date of each review)</i>	08-20-14
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Committee (November 12, 2014)	☐ Not a (b)(2)
❖ NDAs only: Exclusivity Summary <i>(signed by Division Director)</i>	X ☐ 12-2-14
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes X ☐ No

⁴ Filing reviews for scientific disciplines should be filed with the respective discipline.

- This application is on the AIP - If yes, Center Director's Exception for Review memo (<i>indicate date</i>) - If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)	☐ Yes ☒ No ☐
❖ Pediatrics (<i>approvals only</i>) Date reviewed by PeRC _____ If PeRC review not necessary, explain: <u>Because none of the criteria apply to this application and it is exempt.</u>	N/A
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters) (<i>do not include previous action letters, as these are located elsewhere in package</i>)	11-20-14 11-17-14 07-15-14 07-07-14 05-16-14 05-07-14 01-06-14 10-29-13 10-18-13
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	
❖ Minutes of Meetings	
If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	☐ No mtg.
Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	☒ 9-27-12 (PIND 115904)
EOP2 meeting (<i>indicate date of mtg</i>)	☐ No mtg.
Mid-cycle Communication (<i>indicate date of mtg</i>)	☐ N/A
Late-cycle Meeting (<i>indicate date of mtg</i>)	☐ N/A
Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	☐ None
Division Director Summary Review (<i>indicate date for each review</i>)	☒ 08-22-14
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	☒ 08-18-14
PMR/PMC Development Templates (<i>indicate total number</i>)	☐ None
Clinical	
❖ Clinical Reviews	
Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	☐ No separate review
Clinical review(s) (<i>indicate date for each review</i>)	08-18-14
Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	☒ None

❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	Note Clinical review p70; no clinical studies were performed.
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	☐ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	☐ N/A
❖ Risk Management - REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) - REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) - Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	☐ None
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	X ☐ None requested
Clinical Microbiology ☐ None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	☐ No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	X ☐ 06-12-14
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	☐ No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	☐ No separate review
Statistical Review(s) (<i>indicate date for each review</i>)	X ☐ 08-20-14
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	☐ No separate review
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	☐ No separate review
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	X ☐ 08-15-14
❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	☐ None requested
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	☐ No separate review
• Supervisory Review(s) (<i>indicate date for each review</i>)	☐ No separate review
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	X ☐ 05-22-14 07-25-14 (consultation)
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	☐ None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	☐ No carc
❖ ECAC/CAC report/memo of meeting	☐ None
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	☐ None requested

Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	☐ No separate review
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	☐ No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	X ☐ 12-2-14 07-18-14 07-28-14 –Biopharmaceutics
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	X ☐ Sterility -03-09-14
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	X ☐ CDRH Device 08-21-14
❖ Environmental Assessment (check one) (original and supplemental applications)	
☐ Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	07-18-14 (Product Quality review p70)
☐ Review & FONSI <i>(indicate date of review)</i>	
☐ Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Facilities Review/Inspection	
☐ NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within 2 years of action date) <i>(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁵)</i>	Date completed: ☐ Acceptable ☐ Withhold recommendation X ☐ Not applicable
☐ BLAs: TB-EER (date of most recent TB-EER must be within 30 days of action date) <i>(original and supplemental BLAs)</i>	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>	☐ Completed ☐ Requested ☐ Not yet requested X ☐ Not needed (note (Product Quality review p66))

⁵ i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Day of Approval Activities	
❖ For all 505(b)(2) applications: Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☒ No changes ☐ New patent/exclusivity (<i>Notify CDER OND IO</i>)
Finalize 505(b)(2) assessment	☒ 12-1-14
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ 12-2-14
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☐ N/A
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	☐ Done
❖ Ensure Pediatric Record is accurate	☐ N/A
❖ Send approval email within one business day to CDER-APPROVALS	☐ Done

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

/s/

FRANCES V LESANE
12/03/2014

From: LeSane, Frances V
To: ["D.Chmielewski@Lachmanconsultants.com"](mailto:D.Chmielewski@Lachmanconsultants.com)
Bcc: [Mishra, Shrimant](#); [Seggel, Mark R](#)
Subject: RE: NDA 205433 Kitabis Pak - Revised PARI LC PLUS Reusable Nebulizer Label
Date: Thursday, November 20, 2014 1:09:00 PM

Dear Mr. Chmielewski,

We are in agreement that the revised labeling changes of 11-1 7-14 sent to you for the PI and PARI LC PLUS Reusable Nebulizer can be made in the label at the next printing as indicated in February 2015.

If you have any questions, I can be reached at the number below or by email.

Thanks,

Frances for the Review Team for NDA 205433

Frances V. LeSane

Chief, Project Management Staff

Division of Anti-Infective Products

Office of Antimicrobial Products

Center for Drug Evaluation and Research

Phone: 301-796-0747

Fax: 301-796-9881

frances.lesane@fda.hhs.gov

-----Original Message-----

From: D.Chmielewski@Lachmanconsultants.com
[<mailto:D.Chmielewski@Lachmanconsultants.com>]
Sent: Wednesday, November 19, 2014 7:50 AM
To: LeSane, Frances V

Subject: RE: NDA 205433 Kitabis Pak - Revised PARI LC PLUS Reusable Nebulizer Label
Importance: High

Ms. LeSane,

The next commercial batch will be manufactured in late January, early February which would contain the revised proposed labeling. The inventory should be available for marketing end of February.

We hope that this is satisfactory for you.

Please advise as to how I need to submit the accepted revised labeling. Do I do it in a formal submission via the ESG ? Or is acceptance via email satisfactory ?

Thank you for your help.

Donald Chmielewski

Senior Associate

Lachman Consultants

1600 Stewart Avenue, Westbury, NY 11590 (USA)

Telephone: 516-222-6222 Fax: 516-683-1887 Cell: (b) (6)

D.Chmielewski@LachmanConsultants.com

From: "LeSane, Frances V" <Frances.LeSane@fda.hhs.gov>

To: "D.Chmielewski@Lachmanconsultants.com"
<D.Chmielewski@Lachmanconsultants.com>,

Date: 11/18/2014 05:06 PM

Subject: RE: NDA 205433 Kitabis Pak - Revised PARI LC PLUS Reusable

Nebulizer Label

Dear Mr. Chmielewski,

Please let me know when the next printing will be.

Thanks,

Frances

-----Original Message-----

From: D.Chmielewski@Lachmanconsultants.com [
<mailto:D.Chmielewski@Lachmanconsultants.com>]

Sent: Tuesday, November 18, 2014 3:15 PM

To: LeSane, Frances V

Subject: RE: NDA 205433 Kitabis Pak - Revised PARI LC PLUS Reusable

Nebulizer Label

Importance: High

Ms. LeSane,

Since the receipt of the Tentative Approval letter, we have manufactured the validation batches for the drug product which we intend to market. In those batches we used the copy for the printed labeling as was tentatively approved on August 22, 2014.

You have come to us for minor language revisions in the insert for the device component. These changes made the insert more specific to the tobramycin inhalation solution product, instead of generically mentioning a medication [REDACTED] (b) (4)

We accept those changes, and propose that these changes be incorporated at the manufacturing of the next commercial batches. But we hope you will allow the use of the previously submitted device insert for these validation batches which we propose to market once the FINAL APPROVAL is received on December 2, 2014.

Please advise if this proposal to incorporate these changes at the next printing is acceptable.

Enclosed is the copy for the revised device insert, incorporating the recommended changes.

Please advise how you want me to submit this revised insert.

(See attached file: Label PARI LC PLUS Reusable Nebulizer 17NOV14 Changes Accepted.docx)

Donald Chmielewski

Senior Associate

Lachman Consultants

1600 Stewart Avenue, Westbury, NY 11590 (USA)

Telephone: 516-222-6222 Fax: 516-683-1887 Cell: (b) (6)

D.Chmielewski@LachmanConsultants.com

From: "LeSane, Frances V" <Frances.LeSane@fda.hhs.gov>

To: "D.Chmielewski@Lachmanconsultants.com"

<D.Chmielewski@Lachmanconsultants.com>,

Date: 11/17/2014 06:35 PM

Subject: RE: NDA 205433 Kitabis Pak - Revised PARI LC PLUS

Reusable

Nebulizer Label

Dear Mr. Chmielewski,

Please review the attached DRAFT labeling for NDA 205433 PARI LC PLUS Reusable Nebulizer with edits in Track Changes. If there are no additional changes just accept the "Track Changes" and return the label to us ASAP; if you make any changes please send the label back in "Track Changes".

In addition, regarding the Kitabis Pak PI label, please revise section 2.2 (fifth paragraph) to say: Tobramycin inhalation solution should not be diluted or mixed with other drugs including dornase alfa in the nebulizer. Instruct patients on multiple therapies to take their medications prior to inhaling the tobramycin inhalation solution, or as directed by their physician.

If you have any questions, I can be reached at the number below or by email.

Thanks,

Frances for the Review Team for NDA 205433

Frances V. LeSane

Chief, Project Management Staff

Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Phone: 301-796-0747
Fax: 301-796-9881
frances.lesane@fda.hhs.gov

(See attached file: Label PARI LC PLUS Resuable Nebulizer 17NOV14.docx)See our Blog and News/Event Pages! www.LachmanConsultants.com and click on "Blog" or "News" button.

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/s/

FRANCES V LESANE
11/24/2014

From: LeSane, Frances V
To: ["D.Chmielewski@Lachmanconsultants.com"](mailto:D.Chmielewski@Lachmanconsultants.com)
Bcc: [Mishra, Shrimant](#); [Jarikov, Dmitri](#); [Laessig, Katherine A](#); [Nambiar, Sumathi](#)
Subject: RE: NDA 205433 Kitabis Pak - Revised PARI LC PLUS Reusable Nebulizer Label
Date: Monday, November 17, 2014 6:35:00 PM
Attachments: [Label PARI LC PLUS Resuable Nebulizer 17NOV14.docx](#)

Dear Mr. Chmielewski,

Please review the attached DRAFT labeling for NDA 205433 **PARI LC PLUS Reusable Nebulizer** with edits in **Track Changes**. If there are no additional changes just accept the **"Track Changes"** and return the label to us ASAP; if you make any changes please send the label back in **"Track Changes"**.

In addition, regarding the Kitabis Pak PI label, please revise section 2.2 (fifth paragraph) to say: *Tobramycin inhalation solution should not be diluted or mixed with other drugs including dornase alfa in the nebulizer. Instruct patients on multiple therapies to take their medications prior to inhaling the tobramycin inhalation solution, **or as directed by their physician.***

If you have any questions, I can be reached at the number below or by email.

Thanks,

Frances for the Review Team for NDA 205433

Frances V. LeSane

Chief, Project Management Staff

Division of Anti-Infective Products

Office of Antimicrobial Products

Center for Drug Evaluation and Research

Phone: 301-796-0747

Fax: 301-796-9881

frances.lesane@fda.hhs.gov

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

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

/s/

FRANCES V LESANE
11/19/2014



PIND 115904

MEETING MINUTES

PARI Respiratory Equipment, Inc.
Attention: Geoff A. Hunziker
President, eFlow LLC & PRE Holding, Inc.
99 Pacific Street
Suite 155G
Monterey, CA 93940

Dear Mr. Hunziker:

Please refer to your Pre-Investigational New Drug Application (PIND) file for (b) (4)
(Tobramycin Inhalation Solution, USP and PARI LC Plus Reusable Nebulizer).

We also refer to the meeting between representatives of your firm and the FDA on September 27, 2012. The purpose of the meeting was to discuss your proposal to submit a combination product 505(b)(2) marketing application.

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

If you have any questions, call Caroline D. Fukuda, MHA, Regulatory Project Manager, at (301) 796-4757.

Sincerely,

{See appended electronic signature page}

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

Enclosure: Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: September 27, 2012, 9:00 to 10:00 am (EST)
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1415
Silver Spring, Maryland 20903

Application Number: PIND 115904
Product Name: (b) (4) (Tobramycin Inhalation Solution, USP and
PARI LC Plus Reusable Nebulizer)
Indication: management of cystic fibrosis patients with *Pseudomonas
aeruginosa*
Sponsor/Applicant Name: PARI Respiratory Equipment, Inc.

Meeting Chair: John Farley, MD, MPH
Meeting Recorder: Caroline D. Fukuda, MHA

FDA ATTENDEES

Division of Anti-Infective Products (Agency)

Eileen Navarro Almario, MD	Clinical Tem Leader
Kimberly L. Bergman, PharmD	Clinical Pharmacology Team Leader
Peter E. Coderre, PhD, MBA	Clinical Microbiology Reviewer
Steven Donald	Product Quality Microbiology Reviewer
Amy L. Ellis, PhD	Pharmacology/Toxicology Reviewer
John Farley, MD, MPH	Acting Director
Caroline D. Fukuda, MHA	Regulatory Health Project Manager
Christopher Kadoorie, PhD	Statistical Reviewer
Katherine A. Laessig, MD	Deputy Director
Dorota M. Matecka, PhD	CMC Lead/Branch V
Shrimant Mishra, MD, MPH	Medical Officer*
Ryan Owen, PhD	Clinical Pharmacology Reviewer
Wendelyn Schmidt, PhD	Pharmacology/Toxicology Team Leader
Thamban Valappil, PhD	Statistical Team Leader

*participating by telephone

Office of Pharmaceutical Science/Office of New Drug Quality Assessment

Sandra Suarez Sharp, PhD

Biopharmaceutics Reviewer

Office of Combination Products

Patricia Y. Love, MD, MBA

Deputy Director

Center for Device and Radiologic Health, Office of Device Evaluation

Sugato De, MS

Biomedical Engineer

James J Lee, PhD, MSE

Biomedical Engineer

SPONSOR ATTENDEES

PARI Respiratory Equipment, Inc.(PARI)

Donald Chimielewski

Regulatory Consultant, Lachman Consultant Services

Oliver Denk, PhD

Vice President, Business Unit Pharma, PARI Pharma GmbH

(b) (4)

Mike Judge

Director, Operations, PARI Respiratory Equipment, Inc. US

1.0 BACKGROUND

On July 2, 2012, PARI Respiratory Equipment, Inc. requested a Type B pre-New Drug Application (NDA) meeting to discuss PARI's pursuit of a combination product 505(b)(2) NDA application for (b) (4), consisting of Tobramycin Inhalation Solution, USP and cleared to market 510(k) PARI LC Plus Reusable Nebulizer. The reference listed drug (RLD) is TOBI (tobramycin inhalation solution, USP) 300 mg tobramycin and 11.25 mg sodium chloride in sterile water for injection per 5 mL ampule. Included in the meeting request letter were eight questions. PARI submitted a meeting package on August 27, 2012, identical to the July 2, 2012 meeting request letter and the addition of the following five attachments:

Attachment A: LC Plus (b) (4) FDA decision date March 17, 1995 Letter

Attachment B: LC Plus Instructions for Use

Attachment C: LC Plus Technical Drawing

Attachment D: Novartis TOBI Package Insert (the RLD; NDA 050753)

Attachment E: Novartis TOBI Carton and Foil Package Labeling (the RLD)

Preliminary responses were sent to PARI on September 21, 2012. The meeting discussion focused on the Agency's preliminary responses and included clarification and exact

description of the combination product from PARI. The minutes below include PARI's original questions in **bold** font, the Agency's preliminary responses and additional comments in normal font and meeting discussion in blue font. PARI expects to learn what information is needed to submit a 505(b)(2) NDA for this combination product.

2. DISCUSSION

PARI described their intent and the rationale for the development of the (b) (4). The convenience packaging of tobramycin solution for inhalation plus PARI LC Plus Reusable Nebulizer will assure that the patient receives the correct nebulizer (i.e. no chance of nebulizer substitution), the treating physician is assured peace of mind that the nebulizer prescribed is the correct nebulizer, and co-pay and insurance reimbursement issues patients currently experience are eliminated. PARI stated that the inhalation solution is qualitatively and quantitatively (b) (4) TOBI, the RLD. PARI informed the Agency that each (b) (4) will be a carton of 14 pouches (4 vials of Tobramycin Inhalation Solution in each pouch, totaling 56 vials in each carton) and one PARI LC Plus Reusable Nebulizer (subsequently referred to as the Nebulizer).

2.1. Regulatory/Procedural

Question 1: Does the Division agree that the 505(b)(2) submission route is appropriate for an application that will reference the identified Reference Listed Drug and cleared 510(k) device to support efficacy and safety? If not, please comment.

FDA Response to Question 1: It is premature to make this assessment; however, FDA is considering whether a 505(b)(2) or a 505(j) submission is most appropriate. To assist in making this assessment, please identify the specific drug formulation and characteristics in comparison to the reference listed drug (RLD), the name and 510(k) of the compressor, whether PARI will distribute the compressor, and identify all modifications that have been made to the PARI LC Plus Reusable Nebulizer.

The appropriate submission route will be determined by how much the proposed combination product differs from the RLD and 510(k) device(s). In addition, we will consider potential labeling changes that may be needed for the drug and device in the co-package.

Here are particular scenarios that might occur:

- a) If the proposed tobramycin inhalation solution, nebulizer, and compressor are exactly the same as the RLD and its associated cleared nebulizer and compressor, then the abbreviated new drug application (ANDA) submission process could potentially be used.
- b) If there are differences between the proposed tobramycin inhalation solution, nebulizer, and compressor that could affect safety and effectiveness, then further clinical/in-vitro studies might be required. Depending upon the differences and necessary data, then a 505(b)(2) application may be most appropriate.

We defer further assessment of the regulatory pathway until more specific combination product (e.g., drug formulation, information on device modifications, compressor identification) and proposal details are provided and understood.

Discussion: PARI confirmed that the nebulizer is the same device currently on the market and stated that there will be no changes to the device. PARI stated that per the Office of Generic Drugs (OGD), because there is no innovator product for this combination (NDA), an ANDA cannot be submitted. Hence, PARI believes that the appropriate regulatory pathway is submission of a 505(b)(2) NDA.

Regarding the compressor, PARI commented that they have no intention of providing a compressor with the product. PARI stated that they intend for patients to use the DeVilbiss Pulmo-Aide air compressor (subsequently referred to as DeVilbiss compressor) and that the market is saturated with this compressor and added that patients won't have a problem finding a DeVilbiss compressor. PARI further stated that changes to the Instructions for Use labeling of the DeVilbiss compressor will not be proposed.

The Agency asked if PARI's original intent was to develop a product for the generic market. PARI replied that their intent is to provide a combination product and added that the (b) (4) will compete with TOBI, but has the advantage of including the TOBI labeling-recommended nebulizer. The Agency suggested that patent certification and other issues will need to be discussed with the Agency and PARI agreed.

The Agency asked what is the lifespan of the nebulizer. PARI replied that the nebulizer's lifespan is six months. PARI added that as a combination product, a patient would receive a new (b) (4) including a new nebulizer monthly.

2.2. Clinical

Question 2: Is the proposed reference to 21 CFR 320.22(b)(2) and supporting formulation and CMC data sufficient to support a 505(b)(2) NDA filing for tobramycin solution for inhalation, to establish the necessary "clinical bridge" to the Reference Listed Drug? If not, what additional information is required?

FDA Response to Question 2: For your product we do not agree that the "bioavailability/bioequivalence is self evident" as noted in your citation. Preliminarily, however, CFR 320.22(b)3 may be more relevant. This provision states that a waiver of bioequivalence studies is possible when:

(3) *The drug product:*

(i) *Is a solution for application to the skin, an oral solution, elixir, syrup, tincture, a solution for aerosolization or nebulization, a nasal solution, or similar other solubilized form; and*

(ii) *Contains an active drug ingredient in the same concentration and dosage form as a drug product that is the subject of an approved full new drug application or abbreviated new drug application; and*

(iii) Contains no inactive ingredient or other change in formulation from the drug product that is the subject of the approved full new drug application or abbreviated new drug application that may significantly affect absorption of the active drug ingredient or active moiety for products that are systemically absorbed, or that may significantly affect systemic or local availability for products intended to act locally.

For purposes of your combination product, we consider the device constituent parts in this analysis. At this time, however, it is premature to determine if the above regulation is applicable to your combination product. See answer to Question #1.

In addition, the following items should also be met:

1. Inclusion of the biowaiver request as part of the NDA submission.
2. Your proposed product is quantitatively the same as the RLD containing the same amount of NaCl, pH, and osmolality.
3. Your proposed product has equivalent droplet size distribution, emitted dose and other relevant in vitro characterization as the RLD determined using the labeled nebulizer and compressor in accordance with the labeled instructions for use.

Question: Does the Agency require a survey of the available clinical and nonclinical literature, and FDA AERS adverse event database in support of the Integrated Safety Summary for the proposed oral solution drug product? If affirmative, PARI proposes to search the literature back 2 years, and to search the AERS database back 2 years for tobramycin solution for inhalation. Does the Agency concur with this proposal? Will a safety update report for the drug be required?

FDA Response to Question: Please provide recent (within the last three years) tobramycin minimal inhibitory concentration (MIC) susceptibility and resistance data for a minimum of 100 *Pseudomonas aeruginosa* isolates from cystic fibrosis patients. This data may be acquired from the literature.

In addition to a survey of the available clinical and nonclinical literature, please provide a search of the Adverse Event Reporting System (AERS) and Manufacturer and User Facility Device Experience (MAUDE) databases to identify both patient events and product quality events.

Discussion: PARI stated that they will provide references as described above.

PARI stated their intention is to submit a biowaiver request as part of the NDA submission.

PARI described that they detected a slight difference in the osmolality between their product (measured at 167 osmoles per liter (Osm/L)) and the RLD (185 Osm/L); PARI suspects that the RLD is being over-titrated. PARI added that their product's osmolality is within the USP acceptable range for monographs (135 to 200 Osm/L). PARI asked if this is significant. The Agency emphasized that this will be evaluated during the NDA

review and added that if the product's osmolality measures within the USP acceptable range for monographs, this will likely not be an issue.

PARI stated that they will provide results from in vitro cascade impaction studies as part of the NDA submission. The Agency encouraged PARI to dialogue with the Agency prior to starting the cascade impaction testing and PARI agreed.

Question: Does the Division agree that this drug product qualifies for a waiver of the requirement to perform pediatric studies in all pediatric sub populations? If not, please comment.

FDA Response to Question: Clarify whether PARI will be seeking an orphan product designation. Such a designation, if given, would waive the requirement for pediatric studies. Please see 21 CFR 316 for further information.

Discussion:

(b) (4)

Question: If PARI's product is not eligible for a waiver, does the Division agree that pediatric studies can be deferred until after NDA approval?

FDA Response to Question: See above comment.

Discussion: No further discussion.

2.3. Chemistry/Manufacturing/Controls

Question: Can the Division please provide guidance on the supporting documentation that will be required for the 505(b)(2) application for the PARI LC Plus Reusable Nebulizer?

FDA Response to Question: Please refer to recommendations from the Center for Devices and Radiological Health (CDRH), given under "FDA Additional Comments for the Device Constituent Parts."

From the CMC perspective, the application should include results of the product characterization study using a cascade impactor, such as particle/droplet size distribution as per the specified operating parameters and ranges of the proposed device identifying a compressor to be used with the proposed nebulizer. Refer to the Guidance for Industry: Nasal Spray and Inhalation Solution, and Spray Drug Products- Chemistry, Manufacturing and Controls Documentation" (July 2002) for further recommendations for your product characterization.

Discussion: PARI stated that they will provide product characterization as compared to the RLD as part of the NDA.

Question: It is PARI's intention to submit three registration batches of the tobramycin solution for inhalation, finished product release testing, and stability data for the NDA filing. Stability data reported at the time of filing will consist of 6 months at room temperature (25°C, 60% RH) data, 6 months at intermediate storage condition (30°C, 65% RH), and 6 months accelerated (40°C, 75% RH) data. The proposed expiration dating at the time of filing will be (b) (4) months. Does the Division agree with this proposal? If not, please comment.

FDA Response to Question: No, this proposal is not acceptable. We recommend that the NDA include 12-month long-term and 6-month accelerated stability data on three batches of the proposed drug product, tobramycin solution for inhalation, at the time of filing. Please refer to ICH Q1A Guidance for further recommendations regarding the design and testing conditions that should be used in the stability studies for your proposed drug product in the proposed container closure system. The results of in-use stability studies (i.e., for out-of-pouch use) should also be provided to support the proposed storage period and conditions. The proposed expiration dating is a review issue and will be established based on the evaluation of the overall data submitted in the NDA. Please include statistical evaluation of the stability data available for your drug product in your NDA.

Discussion: Regarding stability, PARI agreed to following the aforementioned recommendations.

Additional CMC and Product Quality Microbiology comments:

From the Chemistry Manufacturing and Controls (CMC) perspective, your 505(b)(2) application will need to contain comprehensive CMC information as per 21 CFR 314.50(d)(1) to assure the identity, strength, quality, and purity of your proposed drug substance and drug product. Therefore, Module 3 of your NDA should contain comprehensive information on the characterization, development, manufacturing and quality of the proposed tobramycin drug substance and the drug product. Note that the impurity levels and acceptance criteria proposed in the PARI's drug substance and the drug product specifications will need to be supported by the adequate qualification information. The NDA should also include detailed information on the device to be used for the proposed drug product.

From a Product Quality Microbiology perspective, refer to the 1994 Guidance for Industry for the Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products.

Discussion: PARI stated that the Drug Master File reference will be included as part of the NDA submission.

PARI concurred with the product quality microbiology requirements.

Additional Comments for the Device Constituent Parts

Based on information in the briefing document, we are not able to determine the drug formulation, the name of the compressor, or whether there have been or will be modifications to the (b) (4) PARI LC Plus Reusable Nebulizer. Pending that information, we provide the following comments to evaluate any potential differences.

1. Compressor: The compressor component of a nebulization system has a direct effect on the particle characterization of the delivered drug. Please identify the compressor that is intended for use with the nebulizer in the to-be-marketed configuration of the proposed combination product. Please note that comparative particle characterization studies will be necessary to determine equivalence in performance between the configuration referenced in NDA 050753. Specifically, the effect on particle characterization as a result of the proposed and originally approved compressor (DeVilbiss Pulmo-Aide) will need to be assessed.

Discussion: In regard to particle size distribution, PARI stated that they will provide cascade impaction data. PARI identified the compressor as the DeVilbiss Pulmo-Aide. PARI added that the configuration of the proposed device for their combination product is the same as in the label for the RLD.

2. The current submission contains no performance testing for the nebulizer (including compressor) and drug combination. We evaluate equivalent performance of nebulizers by comparative particle size distribution testing. Please provide comparative particle size delivery test information for both the device under review (finished product, not prototype) and the predicate device. It is recommended that you conduct this testing with a cascade impactor consisting of at least six stages. Because particle size produced by nebulizers is inversely proportional to the gas flow provided to the nebulizer, we recommend that you place a flow meter in line between the compressor and nebulizer, while monitoring and recording the flow during particle size distribution testing of the nebulizers. If the nebulizer is intended for use with a range of flow rates, you must conduct complete particle size distribution testing at the maximum and minimum flow rates. Further, we recommend that you perform a side-by-side particle characterization assessment for the to-be-marketed device and the device configuration used in the clinical trial incorporating the following:
 - a. Approved NDA Configuration: Pari LC Plus Nebulizer, DeVilbiss Pulmo-Aide Compressor, Tobramycin Solution (300 mg/5mL)
 - b. Proposed Configuration: Pari LC Plus Nebulizer, (b) (4) Tobramycin Solution (300 mg/5mL).

We recommend evaluation of the equivalent performance of nebulizers via comparative particle characterization data with a cascade impactor consisting of at least six stages (i.e. Next Generation Cascade Impactor). Laser diffraction is currently not accepted as a standalone method of particle characterization due to concerns regarding reproducibility, specificity, and resolution. Please provide particle characterization data for each of the device configurations cited above with the

proposed formulation of tobramycin using the drug's labeled concentration, dose volume and salt content. Note that each run should continue until the nebulizer is empty, as indicated by sputtering (i.e., erratic aerosolization). In addition, if the specified nebulizers operate over a range of flow rates, it is recommended that data be collected at the minimum and maximum flow rates allowable. Test reports should include the following:

- a. The original nebulizer dose volume in milliliters of drug.
- b. The amount of drug in micrograms recovered on each impactor plate, throat, and outlet filter.
- c. The dead volume in micrograms (the amount of drug remaining in the medication cup when sputtering begins and treatment ends).
- d. The drug mass recovered in the cascade impactor in the respirable size range (i.e., (b) (4), depending on the type of impactor used) expressed as a percent of the total drug mass in the nebulizer cup.
- e. The mass median aerodynamic diameter (MMAD- the diameter above and below which lies 50% of the mass of the particles) of the particles recovered in the impactor.
- f. The geometric standard deviation of the MMAD.

Discussion: In regards to cascade impaction testing, PARI agreed to conducting the recommended testing.

3. In order to adequately evaluate substantial equivalence, sufficient data must be provided to assess potential sources of variability in terms of particle size, total emitted mass and respirable mass that may be attributable to the device. Please note that an adequate number of device samples should be tested in order to assess potential sources of inter-sample variability (drug batch, nebulizer and compressor batches, and manufacturing site etc.). Also, in order to assess intra-sample variability, please provide data demonstrating that single sample of each of the two to-be-marked configurations can deliver the prescribed dose of the proposed drug in a repeatable manner over the intended number of actuations. For each of the two to-be-marketed device configurations, please provide sufficient data to demonstrate that each is able to deliver the prescribed dose in a repeatable manner irrespective of potential sources of inter-sample variability. These data are required to demonstrate that the dosing specifications in your labeling are validated to a specified level of statistical confidence. We recommend that you consider the following recommendations in regards to evaluating potential sources of variability for the proposed combination product:
 - a. Please provide data demonstrating that an individual sample of each of the two proposed device configurations will consistently deliver a specified dose for each (b) (4) dose/dosing regimen tested. In doing so, please validate dose specifications in terms of particle size, total emitted mass, and respirable mass. These data are intended to demonstrate dose repeatability. In your test report, please note the number of runs that were used for each individual device sample-

drug combination, and provide a statistical justification explaining why this number is sufficient to validate the dose specifications in your labeling.

- b. Please provide data characterizing the potential affect of inter-sample variability on the dose specifications in your labeling. Please specify the number of device samples that were used in your performance tests, and provide a statistical analysis explaining why this number of samples is sufficient to demonstrate with an appropriate level of confidence that (1) variability in individual device samples do not noticeably affect the dosing specifications of the proposed device and that (2) develop confidence for particle specifications overall, irrespective of inter-sample variability.
- c. In analyzing the results of the tests cited above, please provide a justification of why the levels of variability shown are appropriate for the use of the devices in delivering the proposed drug formulation.

Discussion: Since the device configuration is the same as for the RLD, PARI suggested that assessment of potential sources of variability does not apply. The Agency agreed.

- 4. If you are indicating the inclusion of a new compressor as an accessory for your combination product, your device may produce particulate matter or potentially toxic vapors or gases into the breathing gas. If the newly proposed compressor introduces new materials (in comparison with the DeVilbiss Pulmo-Aide compressor) into the patient gas pathway, new biocompatibility testing may be required for review. In addition to biocompatibility testing required for an externally communicating device with prolonged tissue contact in accordance with ISO 10993-1, please provide gas sample analysis data to demonstrate that your device adds no carbon monoxide, carbon dioxide, or volatile organic compounds (VOCs), and that the output of particulate matter size 2.5 microns or less are no more than 15 micrograms/cubic meter of air at one atmosphere pressure. The particulate limits correspond to US EPA revised standards. Ozone output must be 0.05 ppm or less (21 CFR 801.415). The emission of volatile organic compounds may be tested using the methods described in ASTM D 5466 or EPA TO-15. If volatile organic compounds are found, the emissions should be eliminated if possible. If emissions of volatile organic compounds cannot be eliminated, the emissions must be explained and shown to have no adverse effects. Particulate matter can be tested by weight of a filter of appropriate retention characteristics. Please state the test methods and results for your device for VOCs, carbon monoxide, carbon dioxide, particulate matter, and ozone. Based on the results of these tests, please provide a comprehensive analysis of the impact of drug-device interaction on biocompatibility.

Discussion and post-meeting note: PARI stated that the compressor flow rates are not adjustable. In follow-up, the Agency confirmed that the evaluation of bioequivalence in terms of droplet size should be conducted at the recommended flow rate for the cascade impactor and not under different flow rates as indicated during

this meeting.

5. Your device labeling is an essential component in communicating the aerosolized therapy dosing specifications of your proposed device. Accordingly, please include the following information in your labeling and provide copies of all updated documentation. Please note that each specification listed in the labeling should have an appropriate level of confidence as demonstrated by your performance testing.
 - a. For (b) (4) dose and controls in your performance testing, please update your proposed labeling with the MMAD, total delivered dose, total respirable dose, respirable fraction and geometric standard deviation (GSD).
 - b. For each specification identified above, please specify a range of values at the specified confidence interval based on statistical analysis of the observed data in your performance testing. For each range of values, please specify the total number of masks, nebulizers, and sample data points used to determine the specified confidence interval.
 - c. We recommend that you characterize particle size using three categories: course particles, fine particles, and extra-fine particles. As a function of the total dose delivered, please include specifications for the total mass and the fraction of each of these size ranges.

Discussion: PARI agreed to adjust their proposed labeling to include the device specifications listed above.

6. Please provide a comprehensive assessment of the lifetime of use of the proposed device. Please provide a specification for the lifetime of use of each individual inhaler unit and information demonstrating that the specified device performance is maintained over the lifetime of the product.

Discussion: PARI described that the nebulizer, on the market since 1993, is labeled to be replaced every 6 months. Within the (b) (4), a 28-day prescription, (b) (4)

PARI will provide life cycle testing for one month as part of the NDA submission.

7. An assessment of device robustness and reliability was not found in the present submission. Please provide a complete assessment of the mechanical safety of the proposed device in accordance with applicable clauses of IEC 60601-1. While the proposed device does not contain electrical components, please note that test reports relating to drop, impact, stability, transportability, temperature, leakage, humidity preconditioning and cleaning are applicable to the proposed device.

Discussion: Regarding assessment of device robustness and reliability, PARI believes this assessment is not applicable. The Agency agreed. PARI stated that they will enhance the device Instructions for Use.

Additional Discussion: The Agency asked if osmolality is the only difference between the RLD and PARI's drug product. PARI stated that they believe all drug product attributes including osmolality, pH, assay and delivery fill, will fall within the acceptable variability ranges and hence match the USP standard.

3.0 PRESCRIBING INFORMATION

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

See the Agency's recommendations for evaluation of bioequivalence under "Additional Comments for the Device Constituent Parts" number 4.

5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Provide the Agency's testing/evaluation criteria for bioequivalence.	FDA	Completed
Submit the protocol for cascade impaction studies.	PARI	When available

Post-Meeting CMC Comment:

Prior to initiating the stability studies for your proposed drug product packaged in the proposed (commercial) container closure system, you are encouraged to submit to the Agency your detailed stability protocol for review and further recommendations.

6.0 ATTACHMENTS AND HANDOUTS

There are no attachments or handouts for the meeting minutes.

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/s/

JOHN J FARLEY
10/26/2012

From: Bhandari, Navdeep
To: D.Chmielewski@lachmanconsultants.com
Subject: RE: NDA 205433 Kitabis Pak Information Request
Date: Tuesday, July 15, 2014 7:23:00 AM
Importance: High

Good Morning Don,

My team has requested the following clarification to your most recent submission:

“The level of (b) (4) is identified only as above the limit (target limit = (b) (4) (b) (4)). However, it is unclear how much the actual level is above the limit. Please indicate the actual amount of (b) (4) detected in the stability samples. Please justify why that level is acceptable.”

Please provide a response as soon as possible.

Thank you,
Navi

-----Original Message-----

From: D.Chmielewski@Lachmanconsultants.com
[<mailto:D.Chmielewski@Lachmanconsultants.com>]
Sent: Friday, July 11, 2014 4:49 PM
To: Bhandari, Navdeep
Cc: LeSane, Frances V
Subject: Re: NDA 205433 Kitabis Pak Information Request

The information was submitted today, July 11 through the ESG.

Enclosed are the documents in that submission.

(See attached file: 1.1.2 FDA Form 356h.pdf)(See attached file: 1.2 Cover Letter.pdf)(See attached file: 3.2.P.7.1.2.7 Leachables Control Rationale Document.pdf)

Donald Chmielewski
Senior Associate
Lachman Consultants
1600 Stewart Avenue, Westbury, NY 11590 (USA)
Telephone: 516-222-6222 Fax: 516-683-1887 Cell: (b) (6)
D.Chmielewski@LachmanConsultants.com

From: "Bhandari, Navdeep" <Navdeep.Bhandari@fda.hhs.gov>
To: "D.Chmielewski@Lachmanconsultants.com" <D.Chmielewski@Lachmanconsultants.com>,
Cc: "LeSane, Frances V" <Frances.LeSane@fda.hhs.gov>
Date: 07/07/2014 12:38 PM
Subject: NDA 205433 Kitabis Pak Information Request

Hello Don,

Please see the following information request from my team:

In the June 19, 2014 submission of leachables results from the 17-month stability time point, actual values are not reported. Please submit the observed results rather than simply noting 'BL' or 'AL'. In addition, please provide a justification for selection of the listed components and justify the proposed Target Limits for each component. Please provide the response by Friday July 11.

Navi

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/s/

NAVDEEP BHANDARI
07/15/2014

From: Bhandari, Navdeep
To: ["D.Chmielewski@Lachmanconsultants.com"](mailto:D.Chmielewski@Lachmanconsultants.com)
Cc: [LeSane, Frances V](#)
Subject: NDA 205433 Kitabis Pak Information Request
Date: Monday, July 07, 2014 12:38:00 PM
Importance: High

Hello Don,

Please see the following information request from my team:

In the June 19, 2014 submission of leachables results from the 17-month stability time point, actual values are not reported. Please submit the observed results rather than simply noting 'BL' or 'AL'. In addition, please provide a justification for selection of the listed components and justify the proposed Target Limits for each component. Please provide the response by Friday July 11.

Navi

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/s/

NAVDEEP BHANDARI
07/07/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 205433

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Pulmoflow Inc.
c/o Lachman Consultants
1600 Stewart Avenue
Westbury, NY 11590

ATTENTION: Donald H. Chmielewski
Senior Associate

Dear Mr. Chmielewski:

Please refer to your New Drug Application (NDA) dated and received, October 2, 2013, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Tobramycin Inhalation Solution, 300 mg.

We also refer to:

- Your correspondence, dated and received, March 5, 2014, requesting review of your proposed proprietary name, Kitabis.
- Our e-mail to you, dated May 7, 2014, noting that a modifier should be added to the proprietary name to help convey that the product has multiple components needed to administer the drug
- Your proprietary name amendment, dated and received, May 12, 2014, adding a modifier to your proposed proprietary name.

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

If any of the proposed product characteristics as stated in your March 5, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Karen Townsend, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5413. For any other information regarding this application, contact Frances LeSane, Regulatory Project Manager in the Office of New Drugs, at (301)796-0747.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

KELLIE A TAYLOR
06/02/2014

From: Townsend, Karen
To: ["D.Chmielewski@Lachmanconsultants.com"](mailto:D.Chmielewski@Lachmanconsultants.com)
Subject: RE: NDA 205433 Information request
Date: Wednesday, May 07, 2014 9:43:00 AM

Dear Mr. Chmielewski,

Thank you for your response.

DMEPA has some information that they have asked me to convey to you regarding the proprietary name review.

DMEPA reviewed the proposed proprietary name Kitabis (Tobramycin) for NDA 205433 and have concerns that the proposed proprietary name does not convey that the product is a co-package containing the drug and a device.

Since your product will always be marketed as a co-package of tobramycin and a nebulizer, we recommend adding a modifier such as "Pak" or "Kit" to the proposed proprietary name to help convey that the product has multiple components needed to administer the drug. Please submit an amendment to the current request for proprietary name review to add a modifier, such as "Pak" or "Kit". We request an official amendment submission by COB May 12, 2014 and a courtesy copy via e-mail as soon as possible to help facilitate review of the name with a modifier. Thank you.

Thank you,
Karen

-----Original Message-----

From: D.Chmielewski@Lachmanconsultants.com [<mailto:D.Chmielewski@Lachmanconsultants.com>]
Sent: Monday, May 05, 2014 9:49 AM
To: Townsend, Karen
Subject: Re: NDA 205433 Information request

Dear Ms. Townsend,

In response to your question, YES, Kitabis will always be copackaged with a nebulizer.

Please do not hesitate to contact me if there are any additional questions.
We greatly appreciate your processing the review for the proposed proprietary name.

Donald Chmielewski
Senior Associate
Lachman Consultants
1600 Stewart Avenue, Westbury, NY 11590 (USA)
Telephone: 516-222-6222 Fax: 516-683-1887 Cell: (b) (6)
D.Chmielewski@LachmanConsultants.com

From: "Townsend, Karen" <Karen.Townsend@fda.hhs.gov>
To: ["D.Chmielewski@lachmanconsultants.com"](mailto:D.Chmielewski@lachmanconsultants.com)
<D.Chmielewski@lachmanconsultants.com>,
Date: 05/05/2014 09:38 AM
Subject: NDA 205433 Information request

Dear Mr.Chmielewski,

Please see the question below that DMEPA has regarding NDA 205433.

During our review of the proposed proprietary name, Kitabis, it is noted that the product is co-packaged with a nebulizer. Can you clarify if Kitabis will always be copackaged with a nebulizer? If not, will patients be switched to another tobramycin inhaled product or will Kitabis also be marketed without the nebulizer? We request a response at your earliest convenience, but no later than COB Wednesday May 7, 2014. Thank you.

Thank you,

Karen

Karen Townsend

Safety Regulatory Project Manager Office
of Surveillance and Epidemiology Center
for Drug Evaluation and Research Food
and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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/s/

KAREN F TOWNSEND
05/29/2014



NDA 205433

INFORMATION REQUEST

Lachman Consultants
Attention: Donald H. Chmielewski (US Agent)
Senior Associate
1600 Stewart Avenue
Westbury, NY 11590

Dear Mr. Chmielewski:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tobramycin Inhalation Solution (300 mg/vial) and LC Plus nebulizer.

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

1. The drug product container closure system consists of a LDPE (b) (4) (b) (4) ampoule in an (b) (4) foil overwrap. While some general information about the (b) (4) (b) (4), as a product that may be chronically administered to patient's lungs, it is critical to demonstrate that leachables are below the Safety Concern Threshold throughout the product shelf-life. This can be achieved by conducting extractables testing followed by leachables testing of stability samples. Please refer to the July 2002 Guidance for Industry: Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products - Chemistry, Manufacturing, and Controls Documentation, and to ICH Guidance on Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances.
2. An acceptance criterion of Not More Than (NMT) (b) (4) % weight change is proposed as part of the drug product specification. A limit of NMT (b) (4) % is not supported by the available stability data, and is inconsistent with ICH Q1A(R2) Guidance for Industry - Stability Testing of New Drug Substances and Products. Please revise the acceptance criterion to NMT (b) (4) % weight change.
3. Even though the product is intended to be stored at (b) (4) C, as an aqueous solution packaged in a semipermeable container, we recommend that weight change be assessed in samples stored at 25°C/40% RH for at least three months.

4. Please provide three (3) sets of drug product samples (labeled ampules in the foil overwrap).

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

Sincerely,

{See appended electronic signature page}

Rapti D. Madurawe, Ph.D.
Branch Chief, Branch V
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

DOROTA M MATECKA
05/16/2014

NDA 205433

INFORMATION REQUEST

Lachman Consultants
Attention: Donald H. Chmielewski (US Agent)
Senior Associate
1600 Stewart Avenue
Westbury, NY 11590

Dear Mr. Chmielewski:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tobramycin Inhalation Solution (300 mg/vial) and LC Plus nebulizer.

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

CDRH - OC

Please provide information regarding how you will show compliance with current good manufacturing practice requirements for your part 4 combination product, Kitabis, as stated in 21 CFR 4.4.

The following deficiencies have been identified while doing the desk review of application NDA 205433, in reference to applicable 21 CFR 820 regulations and manufacturing of the finished combination product, under the assumption that the streamlined approach has been declared, as stated in 21 CFR 4.4(b)(1):

1. There was no information available for review regarding compliance with 21 CFR 820.30, design controls, as they apply to the convenience kit design evaluation.
2. There was no information available for review regarding compliance with 21 CFR 820.50, purchasing controls. Specifically, there was no information regarding the agreements between Pulmoflow and Catalent for the manufacturing of the Kitabis,

(b) (4)

Additionally, there was no information regarding the agreements with PARI Respiratory Equipment, Inc., or any quality control activities implemented on the PARI LC® Plus Reusable Nebulizer.



3. There was no information available for review regarding the establishment of a CAPA system compliant with 21 CFR 820.100.
4. The description of the kitting activities of the finished combination product was inadequate and a proper review of the manufacturing, including packaging of the finished product could not be conducted.

If your firm is not following the streamlined approach as stated in 21 CFR 4.4(b)(1), the submission, NDA205433, may have additional deficiencies.

5. In addition, please indicate if the changes to the LC Plus nebulizer materials described in 3.2.P.4 apply to all LC Plus nebulizers or only to the nebulizers that will be co-packaged with tobramycin inhalation solution.

You may find useful information regarding the types of documents to provide in the document called 'Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff,' (2003). This document may be found at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070897.htm>

Microbiology

6. Provide details of the environmental monitoring program, including methods, areas monitored and alert and action levels. Also provide bioburden alert and action levels for monitoring the bulk drug solution.
7. We acknowledge the generalized SOP for the (b) (4) procedure but specifically identify the production and validation parameters for the (b) (4) procedure used in the sterilization of manufacturing equipment specific to the subject drug product. Identify the specific locations for (b) (4) provide a summary of the specific (b) (4) procedure as well as a summary of the validation results from three recent consecutive, successful runs. If the runs are not relatively recent, provide data from the three most recent requalification runs. Include the results of all controls. Provide the dates of all runs. Provide complete (b) (4) information including manufacturer, lot number, population, confirmed population, (b) (4) and expiration date.
8. We acknowledge the periods identified as hold times but the specific time for each of these periods in the manufacture of the subject drug product is not provided. Provide the maximum time allowed for all holding periods (b) (4) to the completion of filling. Provide validation data to support any excessive holding period.
9. Define the duration of the media fills; all are indicated as being 'non-duration'. Describe

a general plan of action taken in the event of a media fill failure. Briefly describe the investigation as well as the number of repeat fills that are necessary, pending the outcome of the investigation. Indicate disposition of product manufactured both before and after the failed fill. Indicate who is involved in the decision making process.

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

Sincerely,

{See appended electronic signature page}

Rapti D. Madurawe, Ph.D.
Branch Chief, Branch V
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

RAPTI D MADURawe
01/07/2014



NDA 205433

**NDA ACKNOWLEDGEMENT
USER FEES RECEIVED**

Pulmoflow Inc.
c/o Lachman Consultant Services, Inc.
Attention: Donald H. Chmielewski
Senior Associate
1600 Stewart Avenue
Westbury, NY 11590

Dear Mr. Chmielewski:

Please refer to your new drug application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug and Cosmetic Act for Tobramycin Inhalation Solution USP (300 mg/vial) and Pari LC Plus Reusable Nebulizer.

You were notified in our letter dated October 18, 2013, that your application was not accepted for filing due to non-payment of fees. This is to inform you that the Agency has received all required fees and your application has been accepted as of October 23, 2013.

Unless we notify you within 60 days of the above date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on December 22, 2013, in accordance with 21 CFR 314.101(a).

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

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

Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

You did not include such certification when you submitted this application. You may use Form FDA 3674, “Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank,” [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at <http://www.fda.gov/opacom/morechoices/fdaforms/default.html>.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trial(s) referenced in this application. Please note that FDA published a guidance in January 2009, “Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007,” that describes the Agency’s current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at:

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm>. Additional information regarding Title VIII of FDAAA is available at: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html>. Additional information for registering your clinical trials is available at the Protocol Registration System website <http://prsinfo.clinicaltrials.gov/>.

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to **NDA 205433** submitted on October 23, 2013, and that it contains the FDA Form 3674 that was to accompany that application.

If you have already submitted the certification for this application, please disregard the above.

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

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

If you have any questions, contact Frances LeSane, Regulatory Project Manager, at (301) 796-0747.

Sincerely,

{See appended electronic signature page}

Maureen Dillon-Parker
Chief, Project Management Staff
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

MAUREEN P DILLON PARKER
10/29/2013



NDA 205433

UNACCEPTABLE FOR FILING

Pulmoflow Inc.
c/o Lachman Consultant Services, Inc.
Attention: Donald H. Chmielewski
Senior Associate
1600 Stewart Avenue
Westbury, NY 11590

Dear Mr. Chmielewski:

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

Name of Drug Product: Tobramycin Inhalation Solution USP (300 mg/vial) and Pari LC Plus Reusable Nebulizer

Date of Application: September 26, 2013

Date of Receipt: October 02, 2013

Our Reference Number: NDA 205433

Your application was not received until October 2, 2013; therefore, a FY 2014 user fee must be paid for your application.

The full amount of the applicable fee for your application was not received or accepted by FDA prior to October 1, 2013. During the period of the lapse in appropriations, FDA does not have legal authority to accept user fees assessed for FY 2014.

An application is considered incomplete and cannot be accepted for filing until all fees owed have been accepted by FDA. Therefore, this application is not accepted for filing. We will not begin a review of this application's adequacy for filing until FDA accepts the applicable FY 2014 fee.

If you have already initiated payment for the FY 2014 fee for this application during the period of the lapse in appropriations, such as by sending a check or making a wire transfer, then FDA will be able to accept that payment when FDA reopens. Payment should be submitted to the following address:

Food and Drug Administration
P.O. Box 979107
St. Louis, MO 63197-9000

Checks sent by courier should be addressed to:

U.S. Bank
Attention: Government Lockbox 979107
1005 Convention Plaza
St. Louis, MO 63101

When submitting payment for an application fee, include the User Fee I.D. Number, the Application number, and a copy of the user fee coversheet (Form 3397) with your application fee payment. When submitting payment for previously unpaid product and establishment fees, please include the Invoice Number(s) for the unpaid fees and the summary portion of the invoice(s) with your payment. The FDA P.O. Box number (P.O. Box 979107) should be included on any check you submit.

The receipt date for this submission (which begins the review for fileability) will be the date the review division is notified that payment has been received by the bank. Please notify the regulatory project manager indicated below when the appropriate user fees have been sent.

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

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

If you wish to send payment by wire transfer, or if you have any other user fee questions, please call Bev Friedman or Mike Jones at 301-796-3602.

If you have any questions regarding this application, contact Maureen Dillon-Parker, Regulatory Project Manager, at (301) 796-0706.

Sincerely,

{See appended electronic signature page}

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

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/s/

SUMATHI NAMBIAR
10/18/2013