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RESEARCH**

APPLICATION NUMBER:

205433Orig1s000

CHEMISTRY REVIEW(S)

NDA 205433

Kitabis™ Pak
(tobramycin inhalation solution, USP) 300 mg/5 mL
and
Pari LC® Plus Reusable Nebulizer

Pulmoflow, Inc.

Mark R. Seggel
ONDQA
Division of New Drug Quality Assessment II
Branch V

for the Division of Anti-Infective Products

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	4
The Executive Summary	8
I. Recommendations	8
A. Recommendation and Conclusion on Approvability.....	8
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	8
II. Summary of Chemistry Assessments.....	9
A. Description of the Drug Product(s) and Drug Substance(s).....	9
B. Description of How the Drug Product is Intended to be Used.....	10
C. Basis for Approvability or Not-Approval Recommendation.....	11
III. Administrative	13
A. Reviewer's Signature.....	13
B. Endorsement Block.....	13
C. CC Block	13
Chemistry Assessment	14
I. Review of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body of Data.....	14
S DRUG SUBSTANCE	14
P DRUG PRODUCT Tobramycin Inhalation Solution	14
P DRUG PRODUCT Pari LC Plus Reusable Nebulizer	14
A APPENDICES.....	14
R REGIONAL INFORMATION.....	14
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1..	15
A. Labeling & Package Insert	15
B. Environmental Assessment Or Claim Of Categorical Exclusion	16

III. List Of Deficiencies To Be Communicated	16
Iv. Miscellaneous Attachments	16
Attachment A. EES Report.....	16

Chemistry Review Data Sheet

1. NDA 205433
2. REVIEW #: 2
3. REVIEW DATE: 26-NOV-2014
4. REVIEWER: Mark R. Seggel
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u> (eCTD)	<u>Document Date</u>
Original Application (0000)	10/02/13
Amendment (0002) (mfg. facility info.)	11/13/13
Amendment (0003) (product stability update 9-mo.)	12/16/13
Response to information request (0004)	02/24/14
Amendment (0005) (product stability update 12-mo.)	02/27/14
Labeling / Package Insert Draft (0007)	03/21/14
Quality Response To Information Request (0009)	05/09/14
Proprietary Name / Amendment (0010)	05/12/14
Quality Response To Information Request (0011)	05/29/14
Labeling / Container-Carton Draft (0012)	06/11/14
Quality Response To Information Request (0013)	06/19/14
Labeling (0014)	07/10/14
Response (0015) Leachables	07/11/14
Labeling / Foil Pouch (0016)	07/14/14
Response (0017) Leachables	07/17/14
Labeling (0018)	07/18/14
Package Insert and IFU (0019)	07/21/14
Nebulizer Stability (0020)	07/21/14
Package Insert and IFU (0021)	08/07/14
Package Insert and IFU (0022)	08/11/14
Package Insert and IFU (0023)	08/15/14

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u> (eCTD)	<u>Document Date</u>
Resubmission, Class 1 (0028)	10/02/14
Revised device package insert; revised PI/IFU (0029)	11/20/14

Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name:	Pulmoflow, Inc. (a Pari subsidiary)
Address:	3900 Westerre Parkway, Suite 300, Richmond, VA 23233
Representative(s):	Donald H. Chmielewski, Lachman Consultant Services 1600 Stewart Ave , Westbury NY 11590
Telephone:	516-222-6222

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Kitabis™ Pak
- b) Non-Proprietary Name (USAN): tobramycin inhalation solution
- c) Code Name/#: -
- d) CAS Registry Number: CAS-32986-56-4
- e) Chem. Type/Submission Priority:
 - i. Chem. Type: 5
 - ii. Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2) [21 CFR 314.54(a)(1)(vi)]

10. PHARMACOL. CATEGORY: Aminoglycosides - Systemic (4010500);
Antibacterial

11. DOSAGE FORM: Inhalation Solution

12. STRENGTH/POTENCY: 300 mg / Ampule (300 mg / 5 mL)

13. ROUTE OF ADMINISTRATION: Inhalation, Oral

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)

SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR
FORMULA, MOLECULAR WEIGHT

CAS Chemical Name: D-Streptomine, *O*-3-amino-3-deoxy- α -D-glucofuranosyl-(1 \rightarrow 6)-*O*-[2,6-diamino-2,3,6-trideoxy- α -D-ribo-hexopyranosyl-(1 \rightarrow 4)]-2-deoxy-;

Chemistry Review Data Sheet

IUPAC Chemical Name: *O*-3-Amino-3-deoxy- α -D-glucopyranosyl-(1 \rightarrow 4)-*O*-[2,6-diamino-2,3,6-trideoxy- α -D-ribo-hexopyranosyl-(1 \rightarrow 6)]-2-deoxy-L-streptomine.

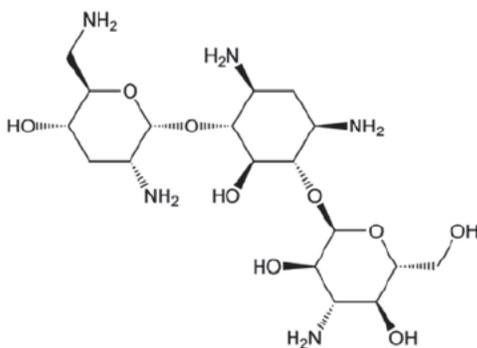
USAN: Tobramycin

UNII Codes: UNII-VZ8RRZ51VK

Molecular Formula: C₁₈H₃₇N₅O₉

Molecular Weight: 467.51

Structural Formula:



17. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	3	Adequate	09/09/13 Y-C.Chen	LoA 07/26/12
	III			3	Adequate	05/17/11 G.Holbert	LoA 08/02/13
	III			3	Adequate	06/30/11 G.Lunn	LoA 08/16/13

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

Chemistry Review Data Sheet

B. Other Documents:

APPLICATION NUMBER	DESCRIPTION	NOTES
NDA 50753	TOBITM (tobramycin inhalation solution); Novartis	LD
Pre-IND 115904	Tobrasol Kit (tobramycin inhalation solution) and Pari LC Plus Nebulizer; Pari	Pre-NDA meeting 09/27/2012

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not applicable		
CDRH ODE	Adequate	21-AUG-2014	James Lee
CDRH OC	Device GMP inspection of Catalent Woodstock recommended.	-	Francisco Vicenty
EES	Acceptable	20-AUG-2014	CDER OC
Pharm/Tox	Approval L/E Acceptable	22-MAY-2014 25-JUL-2014	A.Ellis
ONDQA Biopharmaceutics	Approval (Biowaiver granted)	28-JUL-2014	S. Suarez
LNC	Not applicable	-	
Methods Validation	Not applicable	-	
DMEPA	Proprietary name acceptable Labeling revisions recommended	02-JUN-2014 24-JUN-2014	J.Sheppard A.Winiarski
EA	Categorical Exclusion - Acceptable	this review	-
Quality Microbiology	Recommended for Approval	09-MAR-2014	S.Donald

19. GOAL DATES

GRMP Goal: 18-JUL-2014
PDUFA Goal: 23-AUG-2014
Resubmission User Fee Goal: 02-DEC-2014

The Chemistry Review for NDA 205433

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This Class 1 resubmission of NDA 205433 for the combination product Kitabis Pak is recommended for approval from the CMC perspective.

Protection of the Listed Drug (NDA 50753, Tobramycin Inhalation Solution, Novartis) under U.S. Patent No. 5,508,269 expired on October 18, 2014, allowing full, unconditional approval.

As noted in the previous chemistry review (August 20, 2014), sufficient information to assure the identity, strength, quality, purity, potency and bioavailability of the drug product was provided.

S. Donald concluded that the manufacturing process and controls are acceptable from the quality microbiology perspective. Dr. S. Suarez' has concluded that from the ONDQA Biopharmaceutics perspective the in-vitro characterization of the product and nebulizer (e.g., APSD) adequately demonstrates the bioequivalence of Kitabis Pak to the Listed Drug (LD) TOBI (tobramycin inhalation solution, 300 mg /5 mL). A biowaiver of in vivo BE studies was granted.

Dr. James Lee, CDRH/ODE/DAGIDRDB determined that the device is suitable for the intended purpose, and that a 2-year shelf-life is acceptable. The Catalent Woodstock facility, where the drug product is manufactured, and where the drug and device are co-packaged, was inspected with respect to device GMPs; the facility has acceptable GMP status for profile class DKA.

An overall recommendation of Acceptable was issued by CDER Office of Compliance on 20-AUG-2014 (see attached EES Report).

Since the August 22, 2014 Tentative Approval action, minor changes were made to the package insert and the device insert was revised to make it specific to Kitabis Pak. Overall, the labels and labeling are acceptable from the CMC perspective.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Not applicable.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Kitabis Pak is a convenience pack containing tobramycin inhalation solution, USP, 300 mg / 5 mL, and a Pari LC Plus Reusable Nebulizer. Tobramycin inhalation solution, 300 mg / 5 mL is currently available as TOBI (Novartis, NDA 50753, approved in 1997 [the listed drug]) and as two recently approved generic versions. (b) (4)

(b) (4) This nebulizer is specified in the labeling for all tobramycin inhalation solutions, 300 mg/5 mL, (with the DeVilbiss Pulmo-Aide Compressor. Bethkis (tobramycin inhalation solution 300 mg / 4 mL) is a slightly different formulation approved October 12, 2012 (via NDA 201820) that requires the Pari LC Plus Nebulizer but a different air compressor.

Kitabis Pak tobramycin inhalation solution is manufactured (b) (4)

Critical quality attributes include pH ($6 \pm$ (b) (4)) and osmolality (130-200 mOsmol/kg), which were established for patient tolerability, and sterility. Other quality attributes include tobramycin assay and impurities, and an assay for sodium chloride. The specification is based on the current USP monograph for tobramycin inhalation solution, and is sufficient to assure the identity, strength, quality, purity, potency and bioavailability of the drug product.

To demonstrate 'bioequivalence' of Kitabis Pak tobramycin inhalation solution with TOBI, the applicant provided aerodynamic particle size distribution (APSD) data from both products using specified the Pari LC Plus Nebulizer. Dr. Sandra Suarez, ONDQA Biopharmaceutics reviewer, has determined that the data support granting of a biowaiver.

The overall control strategy includes appropriate limits for drug substance purity, product manufacturing process controls (e.g., control of pH and (b) (4)), maintenance of suitable environmental controls, sterility assurance, and packaging controls. It should be noted that the contract manufacturer, Catalent, for Kitabis Pak tobramycin inhalation solution (b) (4) samples has considerable manufacturing experience with this dosage form, and in fact with this formulation.

Because the inhalation solution is packaged in single-dose semi-permeable LDPE ampules in laminated foil pouches (4 ampules / pouch), extractables testing was performed (b) (4). The extractables characterization report was submitted at our request. At our request, the applicant has also initiated leachables

Executive Summary Section

testing on the registration stability samples. Data from the 17-month time were provided from the ongoing study; additional information about the actual level of (b) (4) observed (simply noted as Above Limit) is forthcoming. Nevertheless, previous experience with the specific LDPE (b) (4), as noted by Dr. Amy Ellis, DAIP Pharm/Tox reviewer] suggests that the material is suitable for use with this product and route of administration.

The Pari LC Plus Reusable Nebulizer was cleared as a Class II device under 510k K935540, dated March 17, 1995. The current version of nebulizer incorporates two new materials of construction; however, these are present in the Pari LC Sprint nebulizer, and are therefore considered adequately qualified from the CDRH-ODE perspective. From the CDRH-ODE perspective, a shelf-life of two years is acceptable for the nebulizer, which is co-packaged with the drug product. The drug product will be labeled for storage for 24 months (b) (4) under refrigeration. It is not expected that refrigeration for 24 (b) (4) months would adversely impact device performance.

Tobramycin is aminoglycoside antibiotic isolated from *Streptomyces tenebrarius* (b) (4)

(b) (4) It was discovered in the late 1950s by scientists at Lilly Research Laboratories along with several other antibiotic factors from *S. tenebrarius*.

Like some other aminoglycosides, tobramycin contains 2-deoxystreptamine and tetrahydropyran rings to which amino groups are attached. Tobramycin is water soluble but is not absorbed from the gastrointestinal tract.

The manufacture of tobramycin drug substance by (b) (4) is adequately documented in Type II DMF (b) (4). Tobramycin is the subject of both USP and EP monographs.

Tobramycin is currently available in injectable dosage forms and in formulations for topical ophthalmic use (tobramycin ophthalmic solution was approved in 1980).

B. Description of How the Drug Product is Intended to be Used

Tobramycin inhalation solution is indicated for the management of cystic fibrosis patients with *P. aeruginosa*. A 300 mg dose is administered twice daily (BID) by oral inhalation using the Pari LC Plus Reusable Nebulizer and DeVilbiss Pulmo-Aide air compressor. Typically, tobramycin is administered twice daily for 28 days, followed by a month off-treatment. Patients 6 years and older receive the same treatment.

The drug product, tobramycin inhalation solution, has a 24-month expiration dating period when stored as directed: Store in a refrigerator at 2°-8°C (36°-46°F). Protect from intense light. Upon removal from the refrigerator, or if refrigeration is

unavailable, tobramycin inhalation solution pouches (opened or unopened) may be stored at room temperature (up to 25°C/77°F) for up to 28 days.

C. Basis for Approvability or Not-Approval Recommendation

The sponsor has provided sufficient information on raw material controls, manufacturing processes and process controls, and adequate specifications for assuring consistent quality of the drug substance and drug product. Drug substance CMC is adequately documented in (b)(4) Type II DMF (b)(4). The NDA, as amended, also has provided sufficient stability information on the drug product to assure strength, purity, and quality of the drug product throughout the expiration dating period.

Tobramycin inhalation solution is filled into LDPE ampules as part of the (b)(4) process. (b)(4) LDPE (b)(4) is used. The filled ampules are packaged in laminated aluminum foil pouches manufactured from (b)(4) foil. Both the LDPE (b)(4) and the foil have been used with other inhalation solution products. Leachables data from the 17-month stability time point was submitted. Following extensive discussions with Dr. Amy Ellis, DAIP Pharm/Tox reviewer, it has been determined that the leachables profile is acceptable (see Memo to NDA 205433 dated 07/25/2014). Leachables testing of stability samples is ongoing.

The Pari LC Plus Reusable Nebulizer is a Class II device and is the subject of a 510(k). CDRH ODE has confirmed the acceptability of the introduction of two new materials of construction.

In vitro performance data (i.e., APSD) was submitted to demonstrate the bioequivalence of Kitabis Pak inhalation solution and TOBI (LD). Based on the review by Dr. Sandra Suarez, ONDQA Biopharmaceutics, a biowaiver from the requirement to perform BE studies was granted.

All facilities (drug substance manufacturing, drug product manufacturing and drug product testing) have acceptable site recommendations with respect to the drug product. Because the drug product manufacturing facility is also responsible for packaging the drug product and the device in the Kitabis Pak convenience kit, CDRH Office of Compliance recommended that Catalent Woodstock be inspected with respect to device GMPs (profile class DKA, (device kit assembler)). That inspection was recently completed. CDER Office of Compliance issued an overall Acceptable recommendation on 20-AUG-2014 (see attached EES Report). Note that CDRH-OC determined that an inspection of the device manufacturer, Pari, Midlothian, Virginia, was not needed.

The analytical procedures used for control of the drug substance and the drug product are adequately described (DMF (b)(4), USP monograph, and USP test methods).

The proprietary name, Kitabis Pak, has been approved for this drug-device combination product. Product labeling was extensively revised following review by DMEPA,

Executive Summary Section

SEALD, Patient Labeling, CDRH and the NDA review team. As revised, the package insert, instructions for use, ampule, foil overwrap and carton labeling are all acceptable from the CMC perspective. Unlike other tobramycin inhalation solution package inserts, the Kitabis Pak insert includes device performance parameters and solution osmolality.

The applicant agreed (ectd seq. no. 0029, 11/20/2014) to revise the nebulizer package insert to reflect specific use with Kitabis Kit tobramycin inhalation solution. The changes will be implemented at the time of the production of the next commercial batches.

See the Chemistry Review dated 20-AUG-2014 for a detailed CMC assessment of the application.

III. Administrative

A. Reviewer's Signature

{electronic signature}

Mark R. Seggel, Chemistry Reviewer

Mark R.

Seggel -A

Digitally signed by Mark R. Seggel -A
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Mark R. Seggel -A,
0.9.2342.19200300.100.1.1=1300071539
Date: 2014.12.01 14:52:57 -05'00'

B. Endorsement Block

{electronic signature}

Dorota Matecka, Ph.D., CMC Lead and Secondary Reviewer

Dorota M.

Matecka -S

Digitally signed by Dorota M.
Matecka -S
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=13001
23291, cn=Dorota M. Matecka -S
Date: 2014.12.01 14:57:19 -05'00'

Rapti D.
Madurawe -A

Digitally signed by Rapti D. Madurawe -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,
ou=People, 0.9.2342.19200300.100.1.1=1300220251,
cn=Rapti D. Madurawe -A
Date: 2014.12.01 15:33:29 -05'00'

{electronic signature}

Rapti Madurawe, Ph.D., Branch Chief

5 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

C. CC Block

Review Team

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

/s/

MARK R SEGCEL

12/02/2014

See Endorsement Block on page 13 for electronic signatures.

NDA 205433

Kitabis™ Pak
(tobramycin inhalation solution, USP) 300 mg/5 mL
and
Pari LC® Plus Reusable Nebulizer

Pulmoflow, Inc.

Mark R. Seggel
ONDQA
Division of New Drug Quality Assessment II
Branch V

for the Division of Anti-Infective Products

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	5
The Executive Summary	9
I. Recommendations	9
A. Recommendation and Conclusion on Approvability	9
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	9
II. Summary of Chemistry Assessments.....	10
A. Description of the Drug Product(s) and Drug Substance(s)	10
B. Description of How the Drug Product is Intended to be Used.....	11
C. Basis for Approvability or Not-Approval Recommendation.....	12
III. Administrative	14
A. Reviewer's Signature.....	14
B. Endorsement Block.....	14
C. CC Block	14
Chemistry Assessment	15
I. Review of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body of Data	15
S DRUG SUBSTANCE	15
S.1 General Information	15
S.1.1 Nomenclature	15
S.1.2 Structure	15
S.1.3 General Properties.....	16
S.2 Manufacture.....	17
S.2.1 Manufacturers	17
S.2.2 Description of Manufacturing Process and Process Controls	17
S.2.3 Control of Materials	17
S.2.4 Controls of Critical Steps and Intermediates.....	17
S.2.5 Process Validation and/or Evaluation	17

S.2.6	Manufacturing Process Development	17
S.3	Characterization.....	18
S.3.1	Elucidation of Structure and other Characteristics.....	18
S.3.2	Impurities	18
S.4	Control of Drug Substance	18
S.4.1	Specification.....	18
S.4.2	Analytical Procedures	20
S.4.3	Validation of Analytical Procedures	20
S.4.4	Batch Analyses.....	20
S.4.5	Justification of Specification.....	20
S.5	Reference Standards or Materials	21
S.6	Container Closure System	21
S.7	Stability	21
P	DRUG PRODUCT Tobramycin Inhalation Solution	22
P.1	Description and Composition of the Drug Product	22
P.2	Pharmaceutical Development	23
P.2.1	Components of the Drug Product.....	24
P.2.1.1	Drug Substance	24
P.2.1.2	Excipients	24
P.2.2	Drug Product	24
P.2.2.1	Formulation Development	24
P.2.2.2	Overages	25
P.2.2.3	Physicochemical and Biological Properties	25
P.2.3	Manufacturing Process Development	30
P.2.4	Container Closure System.....	30
P.2.5	Microbiological Attributes	31
P.2.6	Compatibility.....	31
P.3	Manufacture.....	31
P.3.1	Manufacturers	31
P.3.2	Batch Formula.....	32
P.3.3	Description of Manufacturing Process and Process Controls	33
P.3.4	Controls of Critical Steps and Intermediates.....	35
P.4	Control of Excipients.....	36
P.5	Control of Drug Product.....	37

P.5.1	Specification(s)	37
P.5.2	Analytical Procedures	40
P.5.3	Validation of Analytical Procedures	40
P.5.4	Batch Analyses.....	42
P.5.5	Characterization of Impurities.....	42
P.5.6	Justification of Specification(s).....	44
P.6	Reference Standards or Materials.....	45
P.7	Container Closure System	45
P.8	Stability	54
P.8.1	Stability Summary and Conclusion.....	54
P.8.2	Postapproval Stability Protocol and Stability Commitment.....	57
P.8.3	Stability Data.....	58
P	DRUG PRODUCT Pari LC Plus Reusable Nebulizer	60
A	APPENDICES.....	68
A.1	Facilities and Equipment (biotech only).....	68
A.2	Adventitious Agents Safety Evaluation.....	68
A.3	Novel Excipients	68
R	REGIONAL INFORMATION.....	68
R1	Executed Batch Records	68
R2	Comparability Protocols	68
R3	Methods Validation Package	68
II.	Review Of Common Technical Document-Quality (Ctd-Q) Module 1 ..	69
A.	Labeling & Package Insert	69
B.	Environmental Assessment Or Claim Of Categorical Exclusion	72
III.	List Of Deficiencies To Be Communicated	72
Iv.	Miscellaneous Attachments	72
Attachment A.	EES Report.....	72
Attachment B.	Vial Layout.....	76

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1. NDA 205433
2. REVIEW #: 1 (2) *Updated*
3. REVIEW DATE: 20-AUG-2014
4. REVIEWER: Mark R. Seggel
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Not Applicable	---

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed (eCTD)</u>	<u>Document Date</u>
Original Application (0000)	10/02/13
Amendment (0002) (mfg. facility info.)	11/13/13
Amendment (0003) (product stability update 9-mo.)	12/16/13
Response to information request (0004)	02/24/14
Amendment (0005) (product stability update 12-mo.)	02/27/14
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Labeling / Foil Pouch (0016)	07/14/14
Response (0017) Leachables	07/17/14
Labeling (0018)	07/18/14
Package Insert and IFU (0019)	07/21/14
Nebulizer Stability (0020)	07/21/14
Package Insert and IFU (0021)	08/07/14
Package Insert and IFU (0022)	08/11/14
Package Insert and IFU (0023)	08/15/14

Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name:	Pulmoflow, Inc. (a Pari subsidiary)
Address:	3900 Westerre Parkway, Suite 300, Richmond, VA 23233
Representative(s):	Donald H. Chmielewski, Lachman Consultant Services 1600 Stewart Ave , Westbury NY 11590
Telephone:	516-222-6222

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Kitabis™
- b) Non-Proprietary Name (USAN): tobramycin inhalation solution
- c) Code Name/#: -
- d) CAS Registry Number: CAS-32986-56-4
- e) Chem. Type/Submission Priority:
 - i. Chem. Type: 5
 - ii. Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2) [21 CFR 314.54(a)(1)(vi)]

10. PHARMACOL. CATEGORY: Aminoglycosides - Systemic (4010500);
Antibacterial

11. DOSAGE FORM: Inhalation Solution

12. STRENGTH/POTENCY: 300 mg / Ampule (300 mg / 5 mL)

13. ROUTE OF ADMINISTRATION: Inhalation, Oral

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)

SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR
FORMULA, MOLECULAR WEIGHT

CAS Chemical Name: D-Streptomine, *O*-3-amino-3-deoxy- α -D-glucofuranosyl-(1 \rightarrow 6)-*O*-[2,6-diamino-2,3,6-trideoxy- α -D-ribo-hexopyranosyl-(1 \rightarrow 4)]-2-deoxy-;

IUPAC Chemical Name: *O*-3-Amino-3-deoxy- α -D-glucopyranosyl-(1 \rightarrow 4)-*O*-[2,6-diamino-2,3,6-trideoxy- α -D-ribo-hexopyranosyl-(1 \rightarrow 6)]-2-deoxy-L-streptomine.

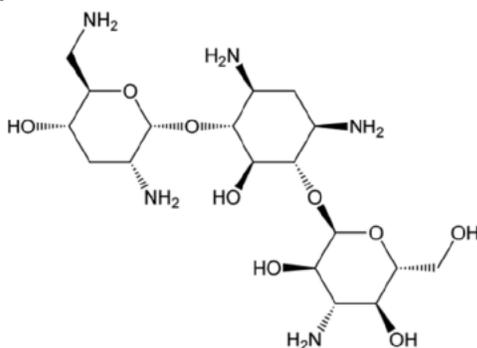
USAN: Tobramycin

UNII Codes: UNII-VZ8RRZ51VK

Molecular Formula: C₁₈H₃₇N₅O₉

Molecular Weight: 467.51

Structural Formula:



17. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	3	Adequate	09/09/13 Y-C.Chen	LoA 07/26/12
	III			3	Adequate	05/17/11 G.Holbert	LoA 08/02/13
	III			3	Adequate	06/30/11 G.Lunn	LoA 08/16/13

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

Chemistry Review Data Sheet

B. Other Documents:

APPLICATION NUMBER	DESCRIPTION	NOTES
NDA 50753	TOBITM (tobramycin inhalation solution); Novartis	LD
Pre-IND 115904	Tobrasol Kit (tobramycin inhalation solution) and Pari LC Plus Nebulizer; Pari	Pre-NDA meeting 09/27/2012

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not applicable		
CDRH ODE	<i>Adequate</i>	19-AUG-2014	<i>James Lee, verbal communication via telephone. Written recommendation forthcoming.</i>
CDRH OC	Device GMP inspection of Catalent Woodstock recommended.	-	Francisco Vicenty
EES	Acceptable	20-AUG-2014	CDER OC
Pharm/Tox	Approval L/E Acceptable	22-MAY-2014 25-JUL-2014	A.Ellis
ONDQA Biopharmaceutics	Approval (Biowaiver granted)	28-JUL-2014	S. Suarez
LNC	Not applicable	-	
Methods Validation	Not applicable	-	
DMEPA	Proprietary name acceptable Labeling revisions recommended	02-JUN-2014 24-JUN-2014	J.Sheppard A.Winiarski
EA	Categorical Exclusion - Acceptable	this review	-
Quality Microbiology	Recommended for Approval	09-MAR-2014	S.Donald

19. GOAL DATES

GRMP Goal: 18-JUL-2014
PDUFA Goal: 23-AUG-2014

The Chemistry Review for NDA 205433

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Kitabis Pak is a combination product consisting of co-packaged tobramycin inhalation solution and a Pari LC Plus nebulizer. Note that the individual components are commercially separately available. The drug product is available from the innovator and at least two generic firms, while the 510(k)-cleared nebulizer is commercially available from Pari for use with these products.

As amended, this NDA has provided sufficient information to assure the identity, strength, quality, purity, potency and bioavailability of the drug product. Labeling review and negotiations have been completed. As revised, the package insert, instructions for use, ampule, foil overwrap and carton labeling are acceptable from the CMC perspective.

S. Donald has concluded that the manufacturing process and controls are acceptable from the quality microbiology perspective. Dr. S. Suarez' has concluded that from the ONDQA Biopharmaceutics perspective the in-vitro characterization of the product and nebulizer (e.g., APSD) adequately demonstrates the bioequivalence of Kitabis Pak to the Listed Drug (LD) TOBI (tobramycin inhalation solution, 300 mg /5 mL). A biowaiver of in vivo BE studies has been granted.

Dr. James Lee, CDRH/ODE/DAGIDRDB has determined that the device is suitable for the intended purpose, and that a 2-year shelf-life is acceptable. Francisco Vicenty, CDRH Office of Compliance, recommended that the Catalent Woodstock facility, where the drug product is manufactured, and where the drug and device are co-packaged, be inspected with respect to device GMPs. That inspection was recently completed; the facility has acceptable GMP status for profile class DKA.

An overall recommendation of Acceptable was issued by CDER Office of Compliance on 20-AUG-2014 (see attached EES Report).

Therefore, from the CMC perspective, this NDA is recommended for approval.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Not applicable.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Kitabis Pak is a convenience pack containing tobramycin inhalation solution, USP, 300 mg / 5 mL, and a Pari LC Plus Reusable Nebulizer. Tobramycin inhalation solution, 300 mg / 5 mL is currently available as TOBI (Novartis, NDA 50753, approved in 1997 [the LD]) and as two recently approved generic versions. (b) (4)

(b) (4) This nebulizer is specified in the labeling for all tobramycin inhalation solutions, 300 mg/5 mL, (with the DeVilbiss Pulmo-Aide Compressor. Bethkis (tobramycin inhalation solution 300 mg / 4 mL) is a slightly different formulation approved October 12, 2012 (via NDA 201820) that requires the Pari LC Plus Nebulizer but a different air compressor.

Kitabis Pak tobramycin inhalation solution is manufactured (b) (4)

Critical quality attributes include pH (6 (b) (4)) and osmolality (130-200 mOsmol/kg), which were established for patient tolerability, and sterility. Other quality attributes include tobramycin assay and impurities, and an assay for sodium chloride. The specification is based on the current USP monograph for tobramycin inhalation solution, and is sufficient to assure the identity, strength, quality, purity, potency and bioavailability of the drug product.

To demonstrate 'bioequivalence' of Kitabis Pak tobramycin inhalation solution with TOBI, the applicant provided aerodynamic particle size distribution (APSD) data from both products using specified the Pari LC Plus Nebulizer. Dr. Sandra Suarez, ONDQA Biopharmaceutics reviewer, has determined that the data support granting of a biowaiver.

The overall control strategy includes appropriate limits for drug substance purity, product manufacturing process controls (e.g., control of pH and (b) (4)), maintenance of suitable environmental controls, sterility assurance, and packaging controls. It should be noted that the contract manufacturer, Catalent, for Kitabis Pak tobramycin inhalation solution (b) (4) samples has considerable manufacturing experience with this dosage form, and in fact with this formulation.

Because the inhalation solution is packaged in single-dose semi-permeable LDPE ampules in laminated foil pouches (4 ampules / pouch), extractables testing was performed (b) (4). The extractables characterization report was submitted at our request. At our request, the applicant has also initiated leachables

Executive Summary Section

testing on the registration stability samples. Data from the 17-month time were provided from the ongoing study; additional information about the actual level of (b) (4) observed (simply noted as Above Limit) is forthcoming. Nevertheless, previous experience with the specific LDPE (b) (4) (b) (4), as noted by Dr. Amy Ellis, DAIP Pharm/Tox reviewer] suggests that the material is suitable for use with this product and route of administration.

The Pari LC Plus Reusable Nebulizer was cleared as a Class II device under 510k K935540, dated March 17, 1995. The current version of nebulizer incorporates two new materials of construction; however, these are present in the Pari LC Sprint nebulizer, and are therefore considered adequately qualified from the CDRH-ODE perspective. From the CDRH-ODE perspective, a shelf-life of two years is acceptable for the nebulizer, which is co-packaged with the drug product. The drug product will be labeled for storage for 24 months (b) (4) under refrigeration. It is not expected that refrigeration for 24 (b) (4) months would adversely impact device performance.

Tobramycin is aminoglycoside antibiotic isolated from *Streptomyces tenebrarius* (b) (4)

(b) (4) It was discovered in the late 1950s by scientists at Lilly Research Laboratories along with several other antibiotic factors from *S. tenebrarius*.

Like some other aminoglycosides, tobramycin contains 2-deoxystreptamine and tetrahydropyran rings to which amino groups are attached. Tobramycin is water soluble but is not absorbed from the gastrointestinal tract.

The manufacture of tobramycin drug substance by (b) (4) is adequately documented in Type II DMF (b) (4). Tobramycin is the subject of both USP and EP monographs.

Tobramycin is currently available in injectable dosage forms and in formulations for topical ophthalmic use (tobramycin ophthalmic solution was approved in 1980).

B. Description of How the Drug Product is Intended to be Used

Tobramycin inhalation solution is indicated for the management of cystic fibrosis patients with *P. aeruginosa*. A 300 mg dose is administered twice daily (BID) by oral inhalation using the Pari LC Plus Reusable Nebulizer and DeVilbiss Pulmo-Aide air compressor. Typically, tobramycin is administered twice daily for 28 days, followed by a month off-treatment. Patients 6 years and older receive the same treatment.

The drug product, tobramycin inhalation solution, has a 24-month expiration dating period when stored as directed: Store in a refrigerator at 2°-8°C (36°-46°F). Protect from intense light. Upon removal from the refrigerator, or if refrigeration is

unavailable, tobramycin inhalation solution pouches (opened or unopened) may be stored at room temperature (up to 25°C/77°F) for up to 28 days.

C. Basis for Approvability or Not-Approval Recommendation

The sponsor has provided sufficient information on raw material controls, manufacturing processes and process controls, and adequate specifications for assuring consistent quality of the drug substance and drug product. Drug substance CMC is adequately documented in (b) (4) Type II DMF (b) (4). The NDA, as amended, also has provided sufficient stability information on the drug product to assure strength, purity, and quality of the drug product throughout the expiration dating period.

Tobramycin inhalation solution is filled into LDPE ampules as part of the (b) (4) (b) (4) process. (b) (4) LDPE (b) (4) is used. The filled ampules are packaged in laminated aluminum foil pouches manufactured from (b) (4) foil. Both the LDPE (b) (4) and the foil have been used with other inhalation solution products. Leachables data from the 17-month stability time point was submitted. Following extensive discussions with Dr. Amy Ellis, DAIP Pharm/Tox reviewer, it has been determined that the leachables profile is acceptable (see Memo to NDA 205433 dated 07/25/2014). Leachables testing of stability samples is ongoing.

The Pari LC Plus Reusable Nebulizer is a Class II device and is the subject of a 510(k). CDRH ODE has confirmed the acceptability of the introduction of two new materials of construction.

In vitro performance data (i.e., APSD) was submitted to demonstrate the bioequivalence of Kitabis Pak inhalation solution and TOBI (LD). Dr. Sandra Suarez, ONDQA Biopharmaceutics, has recommended that a biowaiver from the requirement to perform BE studies be granted.

All facilities (drug substance manufacturing, drug product manufacturing and drug product testing) have acceptable site recommendations with respect to the drug product. Because the drug product manufacturing facility is also responsible for packaging the drug product and the device in the Kitabis Pak convenience kit, CDRH Office of Compliance recommended that Catalent Woodstock be inspected with respect to device GMPs (profile class DKA, (device kit assembler)). That inspection was recently completed. CDER Office of Compliance issued an overall Acceptable recommendation on 20-AUG-2014 (see attached EES Report). Note that CDRH-OC determined that an inspection of the device manufacturer, Pari, Midlothian, Virginia, was not needed.

The analytical procedures used for control of the drug substance and the drug product are adequately described (DMF (b) (4), USP monograph, and USP test methods).

The proprietary name, Kitabis Pak, has been approved for this drug-device combination product. Product labeling was extensively revised following review by DMEPA,

Executive Summary Section

SEALD, Patient Labeling, CDRH and the NDA review team. As revised, the package insert, instructions for use, ampule, foil overwrap and carton labeling are all acceptable from the CMC perspective. Unlike other tobramycin inhalation solution package inserts, the Kitabis Pak insert includes device performance parameters and solution osmolality.

III. Administrative

A. Reviewer's Signature

{see electronic signature page}
Mark R. Seggel, Chemistry Reviewer

B. Endorsement Block

{see electronic signature page}
Dorota Matecka, Ph.D., CMC Lead and Secondary Reviewer

{see electronic signature page}
Rapti Madurawe, Ph.D., Branch Chief

C. CC Block

{see DARRTS}

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

/s/

MARK R SEGCEL
08/20/2014

DOROTA M MATECKA
08/20/2014

RAPTI D MADURawe
08/20/2014

NDA 205433

**Kitabis™ Pak
(tobramycin inhalation solution, USP) 300 mg/5 mL
and
Pari LC® Plus Reusable Nebulizer**

Pulmoflow, Inc.

**Mark R. Seggel
ONDQA
Division of New Drug Quality Assessment II
Branch V**

for the Division of Anti-Infective Products

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	5
The Executive Summary	9
I. Recommendations	9
A. Recommendation and Conclusion on Approvability	9
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	9
II. Summary of Chemistry Assessments.....	9
A. Description of the Drug Product(s) and Drug Substance(s)	9
B. Description of How the Drug Product is Intended to be Used.....	11
C. Basis for Approvability or Not-Approval Recommendation.....	11
III. Administrative	13
A. Reviewer's Signature.....	13
B. Endorsement Block.....	13
C. CC Block	13
Chemistry Assessment	14
I. Review of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body of Data	14
S DRUG SUBSTANCE	14
S.1 General Information	14
S.1.1 Nomenclature	14
S.1.2 Structure	14
S.1.3 General Properties.....	15
S.2 Manufacture.....	16
S.2.1 Manufacturers	16
S.2.2 Description of Manufacturing Process and Process Controls	16
S.2.3 Control of Materials	16
S.2.4 Controls of Critical Steps and Intermediates.....	16
S.2.5 Process Validation and/or Evaluation	16

S.2.6	Manufacturing Process Development	16
S.3	Characterization.....	17
S.3.1	Elucidation of Structure and other Characteristics.....	17
S.3.2	Impurities	17
S.4	Control of Drug Substance	17
S.4.1	Specification.....	17
S.4.2	Analytical Procedures	18
S.4.3	Validation of Analytical Procedures	18
S.4.4	Batch Analyses.....	19
S.4.5	Justification of Specification.....	19
S.5	Reference Standards or Materials.....	19
S.6	Container Closure System	20
S.7	Stability	20
P	DRUG PRODUCT Tobramycin Inhalation Solution	21
P.1	Description and Composition of the Drug Product	21
P.2	Pharmaceutical Development	22
P.2.1	Components of the Drug Product.....	23
P.2.1.1	Drug Substance	23
P.2.1.2	Excipients	23
P.2.2	Drug Product	23
P.2.2.1	Formulation Development	23
P.2.2.2	Overages	24
P.2.2.3	Physicochemical and Biological Properties	24
P.2.3	Manufacturing Process Development	29
P.2.4	Container Closure System.....	29
P.2.5	Microbiological Attributes	30
P.2.6	Compatibility.....	30
P.3	Manufacture.....	30
P.3.1	Manufacturers	30
P.3.2	Batch Formula.....	31
P.3.3	Description of Manufacturing Process and Process Controls	32
P.3.4	Controls of Critical Steps and Intermediates.....	34
P.4	Control of Excipients.....	35
P.5	Control of Drug Product.....	36

P.5.1	Specification(s)	36
P.5.2	Analytical Procedures	39
P.5.3	Validation of Analytical Procedures	39
P.5.4	Batch Analyses.....	41
P.5.5	Characterization of Impurities.....	42
P.5.6	Justification of Specification(s).....	43
P.6	Reference Standards or Materials.....	44
P.7	Container Closure System	44
P.8	Stability	53
P.8.1	Stability Summary and Conclusion.....	53
P.8.2	Postapproval Stability Protocol and Stability Commitment.....	56
P.8.3	Stability Data.....	57
P	DRUG PRODUCT Pari LC Plus Reusable Nebulizer	59
A	APPENDICES.....	66
A.1	Facilities and Equipment (biotech only).....	66
A.2	Adventitious Agents Safety Evaluation.....	66
A.3	Novel Excipients	66
R	REGIONAL INFORMATION.....	66
R1	Executed Batch Records	66
R2	Comparability Protocols	66
R3	Methods Validation Package	66
II.	Review Of Common Technical Document-Quality (Ctd-Q) Module 1..	67
A.	Labeling & Package Insert	67
B.	Environmental Assessment Or Claim Of Categorical Exclusion	70
III.	List Of Deficiencies To Be Communicated	70
Iv.	Miscellaneous Attachments	70
Attachment A.	EES	70
Attachment B.	Vial Layout – Pari -5 mL Round Vial – (b) (4)	71

Chemistry Review Data Sheet

1. NDA 205433
2. REVIEW #: 1
3. REVIEW DATE: 18-JUL-2014
4. REVIEWER: Mark R. Seggel
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Not Applicable	---

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed (eCTD)</u>	<u>Document Date</u>
Original Application (0000)	10/02/13
Amendment (0002) (mfg. facility info.)	11/13/13
Amendment (0003) (product stability update 9-mo.)	12/16/13
Response to information request (0004)	02/24/14
Amendment (0005) (product stability update 12-mo.)	02/27/14
Labeling / Package Insert Draft (0007)	03/21/14
Quality Response To Information Request (0009)	05/09/14
Proprietary Name / Amendment (0010)	05/12/14
Quality Response To Information Request (0011)	05/29/14
Labeling / Container-Carton Draft (0012)	06/11/14
Quality Response To Information Request (0013)	06/19/14
Labeling (0014)	07/10/14
Response (0015) Leachables	07/11/14
Labeling / Foil Pouch (0016)	07/14/14

7. NAME & ADDRESS OF APPLICANT:

Name:	Pulmoflow, Inc. (a Pari subsidiary)
Address:	3900 Westerre Parkway, Suite 300, Richmond, VA 23233
Representative(s):	Donald H. Chmielewski, Lachman Consultant Services 1600 Stewart Ave , Westbury NY 11590
Telephone:	516-222-6222

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Kitabis™
- b) Non-Proprietary Name (USAN): tobramycin inhalation solution
- c) Code Name/#: -
- d) CAS Registry Number: CAS-32986-56-4
- e) Chem. Type/Submission Priority:
 - i. Chem. Type: 5
 - ii. Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2) [21 CFR 314.54(a)(1)(vi)]

10. PHARMACOL. CATEGORY: Aminoglycosides - Systemic (4010500);
Antibacterial

11. DOSAGE FORM: Inhalation Solution

12. STRENGTH/POTENCY: 300 mg / Ampule (300 mg / 5 mL)

13. ROUTE OF ADMINISTRATION: Inhalation, Oral

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)

 SPOTS product – Form Completed Not a SPOTS product16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR
FORMULA, MOLECULAR WEIGHT

CAS Chemical Name: D-Streptomine, *O*-3-amino-3-deoxy- α -D-glucopyranosyl-(1 \rightarrow 6)-*O*-[2,6-diamino-2,3,6-trideoxy- α -D-*ribo*-hexopyranosyl-(1 \rightarrow 4)]-2-deoxy-;

IUPAC Chemical Name: *O*-3-Amino-3-deoxy- α -D-glucopyranosyl-(1 \rightarrow 4)-*O*-[2,6-diamino-2,3,6-trideoxy- α -D-*ribo*-hexopyranosyl-(1 \rightarrow 6)]-2-deoxy-L-streptomine.

USAN: Tobramycin

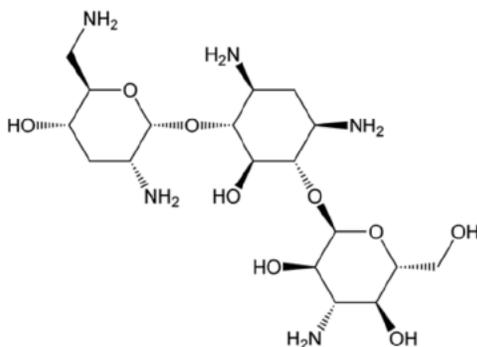
UNII Codes: UNII-VZ8RRZ51VK

Molecular Formula: C₁₈H₃₇N₅O₉

Molecular Weight: 467.51

Chemistry Review Data Sheet

Structural Formula:



17. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	3	Adequate	09/09/13 Y-C.Chen	LoA 07/26/12
	III			3	Adequate	05/17/11 G.Holbert	LoA 08/02/13
	III			3	Adequate	06/30/11 G.Lunn	LoA 08/16/13

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

APPLICATION NUMBER	DESCRIPTION	NOTES
NDA 50753	TOBITM (tobramycin inhalation solution); Novartis	LD
Pre-IND 115904	Tobrasol Kit (tobramycin inhalation solution) and Pari LC Plus Nebulizer; Pari	Pre-NDA meeting 09/27/2012

Chemistry Review Data Sheet

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not applicable		
CDRH ODE	<i>Pending</i>	<i>Pending</i>	James Lee
CDRH OC	<i>Pending</i>	<i>Pending</i>	Francisco Vicenty
EES	<i>Pending</i>	<i>Pending</i>	Steve Hertz, CDER OC
Pharm/Tox	Approval*	22-MAY-2014	A.Ellis
ONDQA Biopharmaceutics	Acceptable (Biowaiver granted)	-	S. Suarez
LNC	Not applicable		
Methods Validation	Not applicable	-	
DMEPA	Proprietary name acceptable Labeling revisions recommended <i>Revised Labeling</i>	02-JUN-2014 24-JUN-2014 <i>Pending</i>	J.Sheppard A.Winiarski ???
EA	Categorical Exclusion - Acceptable	this review	
Quality Microbiology	Recommended for Approval	09-MAR-2014	S.Donald

* "...provided that the Chemistry Reviewer agrees with the sponsor's assessment that the product contains no impurities or degradation products that need to be qualified via nonclinical testing."

19. GOAL DATES

GRMP Goal: 18-JUL-2014
PDUFA Goal: 23-AUG-2014

The Chemistry Review for NDA 205433

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

In general, this NDA, as amended, has provided sufficient information to assure the identity, strength, quality, purity, potency and bioavailability of the drug product. However, additional information regarding leachables in the drug product is forthcoming.

S. Donald has concluded that the manufacturing process and controls are acceptable from the quality microbiology perspective. Dr. S. Suarez' has concluded that from the ONDQA Biopharmaceutics perspective the in-vitro characterization of the product and nebulizer (e.g., APSD) adequately demonstrates the bioequivalence of Kitabis Pak to the Listed Drug (LD) TOBI (tobramycin inhalation solution, 300 mg /5 mL)

Final recommendations from CDRH-ODE and CDRH Office of Compliance regarding the Pari LC Plus Reusable Nebulizer are pending.

The final overall CDER Office of Compliance recommendation is pending, although the facilities apparently have acceptable CGMP status, at least from the drug manufacturing perspective.

Therefore, from the CMC perspective, this NDA is currently not recommended for approval.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Not applicable.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Kitabis Pak is a convenience pack containing tobramycin inhalation solution, USP, 300 mg / 5 mL, and a Pari LC Plus Reusable Nebulizer. Tobramycin inhalation solution, 300 mg / 5 mL is currently available as TOBI (Novartis, NDA 50753, approved in 1997 [the LD]) and as two recently approved generic versions. (b) (4)

This nebulizer is specified in the labeling for all tobramycin inhalation solutions, 300 mg/5 mL, (with the DeVilbiss

Executive Summary Section

Pulmo-Aide Compressor. Bethkis (tobramycin inhalation solution 300 mg / 4 mL) is a slightly different formulation approved October 12, 2012 (via NDA 201820) that requires the Pari LC Plus Nebulizer but a different air compressor.

Kitabis Pak tobramycin inhalation solution is manufactured (b) (4)

Critical quality attributes include pH (6 (b) (4)) and osmolality (130-200 mOsmol/kg), which were established for patient tolerability, and sterility. Other quality attributes include tobramycin assay and impurities, and an assay for sodium chloride. The specification is based on the current USP monograph for tobramycin inhalation solution, and is sufficient to assure the identity, strength, quality, purity, potency and bioavailability of the drug product.

To demonstrate 'bioequivalence' of Kitabis Pak tobramycin inhalation solution with TOBI, the applicant provided aerodynamic particle size distribution (APSD) data from both products using specified the Pari LC Plus Nebulizer. Dr. Sandra Suarez, ONDQA Biopharmaceutics reviewer, has determined that the data support granting of a biowaiver.

The overall control strategy includes appropriate limits for drug substance purity, product manufacturing process controls (e.g., control of pH and (b) (4)), maintenance of suitable environmental controls, sterility assurance, and packaging controls. It should be noted that the contract manufacturer, Catalent, for Kitabis Pak tobramycin inhalation solution (b) (4) samples has considerable manufacturing experience with this dosage form, and in fact with this formulation.

Because the inhalation solution is packaged in single-dose semi-permeable LDPE ampules in laminated foil pouches (4 ampules / pouch), extractables testing was performed (b) (4). The extractables characterization report was submitted at our request. At our request, the applicant has also initiated leachables testing on the registration stability samples. Data from the 17-month time were provided from the ongoing study; additional information about the actual level of (b) (4) observed (simply noted as Above Limit) is forthcoming. Nevertheless, previous experience with the specific LDPE (b) (4) (b) (4), as noted by Dr. Amy Ellis, DAIP Pharm/Tox reviewer] suggests that the material is suitable for use with this product and route of administration.

The Pari LC Plus Reusable Nebulizer was cleared as a Class II device under 510k K935540, dated March 17, 1995. The current version of nebulizer incorporates two new materials of construction; however, these are present in the Pari LC Sprint

nebulizer, and are therefore considered adequately qualified from the CDRH-ODE perspective. A shelf-life for the nebulizer needs to be established to allow co-packaging with the drug product, which will be labeled for storage for 24 months (b) (4) under refrigeration. It is not expected that refrigeration for 24- (b) (4) months would adversely impact device performance.

Tobramycin is aminoglycoside antibiotic isolated from *Streptomyces tenebrarius* (b) (4). It was discovered in the late 1950s by scientists at Lilly Research Laboratories along with several other antibiotic factors from *S. tenebrarius*.

Like some other aminoglycosides, tobramycin contains 2-deoxystreptamine and tetrahydropyran rings to which amino groups are attached. Tobramycin is water soluble but is not absorbed from the gastrointestinal tract.

The manufacture of tobramycin drug substance by (b) (4) is adequately documented in Type II DMF (b) (4). Tobramycin is the subject of both USP and EP monographs.

Tobramycin is currently available in injectable dosage forms and in formulations for topical ophthalmic use (tobramycin ophthalmic solution was approved in 1980).

B. Description of How the Drug Product is Intended to be Used

Tobramycin inhalation solution is indicated for the management of cystic fibrosis patients with *P. aeruginosa*. A 300 mg dose is administered twice daily (BID) by oral inhalation using the Pari LC Plus Reusable Nebulizer and DeVilbiss Pulmo-Aide air compressor. Typically, tobramycin is administered twice daily for 28 days, followed by a month off-treatment. Patients 6 years and older receive the same treatment.

The drug product, tobramycin inhalation solution, has a 24-month expiration dating period when stored as directed: Store in a refrigerator at 2°-8°C (36°-46°F). Protect from intense light. Upon removal from the refrigerator, or if refrigeration is unavailable, tobramycin inhalation solution pouches (opened or unopened) may be stored at room temperature (up to 25°C/77°F) for up to 28 days.

C. Basis for Approvability or Not-Approval Recommendation

The sponsor has provided sufficient information on raw material controls, manufacturing processes and process controls, and adequate specifications for assuring consistent quality of the drug substance and drug product. Drug substance CMC is adequately documented in (b) (4) Type II DMF (b) (4). The NDA, as amended, also has provided sufficient stability information on the drug product to assure strength, purity, and quality of the drug product throughout the expiration dating period.

Executive Summary Section

Tobramycin inhalation solution is filled into LDPE ampules as part of the (b) (4) process. (b) (4) LDPE (b) (4) is used. The filled ampules are packaged in laminated aluminum foil pouches manufactured from (b) (4) foil. Both the LDPE (b) (4) and the foil have been used with other inhalation solution products. *Leachables/extractables testing is ongoing. Leachables data from the 17-month stability time point has been received but further clarification has been requested. Discussions with Dr. Amy Ellis, DAIP Pharm/Tox reviewer regarding the suitability of the packaging components are ongoing.*

The Pari LC Plus Reusable Nebulizer is a Class II device and is the subject of a 510(k). CDRH ODE has been consulted to confirm the adequacy of the device documentation, and the acceptability of the introduction of two new materials of construction.

In vitro performance data (i.e., APSD) was submitted to demonstrate the bioequivalence of Kitabis Pak inhalation solution and TOBI (LD). The data are under review by Dr. Sandra Suarez, ONDQA Biopharmaceutics.

All facilities (drug substance manufacturing, drug product manufacturing and drug product testing) have acceptable site recommendations, although a final overall recommendation has not been issued by the Office of Compliance. Because the drug product manufacturing facility is also responsible for packaging the drug product and the device in the Kitabis Pak convenience kit, a CDRH-OC recommendation regarding compliance with device GMPs has been requested.

The analytical procedures used for control of the drug substance and the drug product are adequately described (DMF (b) (4), USP monograph, and USP test methods).

The proprietary name, Kitabis Pak, has been approved for this drug-device combination product. Labeling is currently under review by DMEPA, SEALD and the NDA review team. An addendum to this review will be filed covering the final labeling.

III. Administrative**A. Reviewer's Signature**

{see electronic signature page}
Mark R. Seggel, Chemistry Reviewer

B. Endorsement Block

{see electronic signature page}
Dorota Matecka, Ph.D., CMC Lead and Secondary Reviewer

C. CC Block

{see DARRTS}

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

/s/

MARK R SEGCEL
07/17/2014

DOROTA M MATECKA
07/18/2014