CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201820Orig1s000

CHEMISTRY REVIEW(S)

NDA 201-820
Tobramycin Inhalation Solution

Chiesi Pharmaceuticals, Inc.

Review 3

Shrikant Pagay, Ph.D.
Chemistry Reviewer

Office of New Drug Quality Assessment

For the Division of Anti-Infective Products

The Chemistry Review for NDA 201-820

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 201-820 has provided sufficient information to assure the identity, strength, purity, and quality of the drug product. This NDA is recommended for approval from the CMC perspective pending the satisfactory resolution of the device bridging studies by CDRH.

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

NA

II. Summary of Chemistry Assessments

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

Drug Substance:
Tobramycin is an aminoglycoside antibiotic with bactericidal activity against a broad spectrum of gram-negative bacteria including *Pseudomonas aeruginosa* which is the primary cause of lung infections in CF patients. It inhibits bacterial protein synthesis. The drug substance is [redacted (b) (4)]. It is supplied as a [redacted (b) (4)]. Tobramycin is well characterized for the related substances and degradation products. It is freely soluble in water [redacted (b) (4)] Tobramycin sulfate has been approved previously in several dosage forms including inhalation solution. Tobramycin is supplied as a [redacted (b) (4)] drug substance; however, the endotoxin level in the drug substance is controlled.

Drug Product:
Tobramycin inhalation solution is a sterile aqueous solution of tobramycin, sulfuric acid, sodium chloride, sodium hydroxide and water for injection. Sulfuric acid is used to [redacted (b) (4)]. For adjusting the pH, sodium hydroxide solution was used. Sodium chloride is [redacted (b) (4)] and water for injection [redacted (b) (4)]. No preservatives are used in the formulation. [redacted (b) (4)] was used throughout the manufacturing process. Tobramycin solution was prepared [redacted (b) (4)]. The solution was filtered using [redacted (b) (4)] Appropriate in-process controls are used in the preparation of tobramycin [redacted (b) (4)]

(b) (4). The primary container is a clear, low density polyethylene unit dose ampoule. The secondary container is a pre-printed (b) (4) Each pouch contains one strip of four unit-dose ampoules. A 28 days treatment package is a box containing 14 over-pouches, corresponding to 56 single-dose containers, and a printed package leaflet. The drug product is stored in refrigerator at 36-46 °F/2-8 °C. When the product is removed for administration, the in-use storage condition is 25°C. The shelf life is 24 months under refrigeration condition and 28 days under room temperature. Sufficient stability data is provided to support the claim for setting the expiration date.

Since tobramycin is highly toxic, when administered by IV, sufficient drug level in lungs is difficult to achieve without reaching the toxic level. When administered by inhalation, sufficient drug is delivered in lungs with only minimum systemic absorption through inhalation route.

Formulation Differences between this NDA and Reference Listed Drug (RLD)
The proposed osmolality, pH and absorbance of this formulation are different than for the RLD which is Tobi Inhalation Solution approved in 1997. Osmolality of this formulation is between the osmolality of (b) (4) and Tobi. Also the pH is slightly different than for Tobi; however, both drug products are controlled in the acidic pH range. Limit for absorbance is slightly higher than for the RLD. These differences may relate to the differences in concentration of tobramycin in the 2 drug products. The proposed formulation is at a higher concentration than Tobi. If there are no issues with any adverse events that relate to these differences, then minor differences in osmolality, pH and absorbance between the NDA formulation and RLD are acceptable.

Drug Delivery Device:
Tobramycin is delivered by inhalation route using a compressor pump and a nebulizer. The proposed device for marketing is different than the ones used during the clinical trial. Since the devices are approved under the Center for Devices (CDRH), this is being reviewed by CDRH as a consult. From the quality perspective, the studies performed to characterize the droplet size distribution of the inhalation solution are adequate. However, it is not clear if in-vitro characterization of droplet size distribution alone is sufficient to bridge differences between clinical and commercial devices. .

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

The inhalation solution is delivered for the topical application to lungs as a fine mist through a compressor and nebulizer. The label provides complete instructions for the drug administration and device cleaning for reuse for the next dosing.

C. Basis for Approvability or Not-Approval Recommendation

All manufacturing and control facilities were found Acceptable by the Office of Compliance on 13th June 2012.

The sponsor has provided satisfactory response to the information requests on 1/21/2011 and 5/13/2011.

The updated stability data on 3 primary batches support the proposed shelf life.

Pending

- Demonstration of equivalence between the clinical device and the proposed commercial device regarding delivery of the inhalation solution (CDRH Consult)

III. Administrative

A. Reviewer's Signature: Shrikant N. Pagay

B. Endorsement Block

Chemistry Branch Chief: Name /Date: Rapti Madurawe

C. CC Block

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/s/

SHRIKANT N PAGAY
08/31/2012
Review 3

RAPTI D MADURAWE
08/31/2012

Review #2

NDA 201-820

Tobramycin Inhalation Solution
Chiesi Pharmaceuticals, Inc.

Date : 17 August, 2011

Shrikant Pagay
Chemistry Reviewer
Office of New Drug Quality Assessment

Recommendation

NDA 201-820 has provided sufficient information to assure identity, strength, purity, and quality of the drug product. This NDA is recommended for approval from the CMC perspective pending the satisfactory resolution of the device bridging studies (CDRH) and the labeling negotiations.

Basis for Approvability or Not-Approval Recommendation

All manufacturing and control facilities are Acceptable to the Office of Compliance. The sponsor has provided a satisfactory response to information requests on 1/21/2011 and 5/13/2011. The quality microbiology reviewer has found the microbiology component of the CMC-submission satisfactory. Also, stability study update for 24 months, the proposed shelf life was received on 6/10/2011, and is satisfactory. Prior to approval, the following pending issues must be satisfactorily concluded:

- Demonstration of equivalence between the clinical device and the proposed commercial device regarding delivery of the inhalation solution (CDRH Consult)
- Labeling negotiations (Review Team)

Review #2 Summary:

Quality Review #1 dated 6/24/2011 recommended this application for approval from the CMC perspective pending satisfactory resolution of the device bridging studies (CDRH), the quality microbiology evaluation, and the labeling negotiations.

On 7/8/2011 Dr. Robert Mello, Quality Microbiologist, provided a consult review indicating the application is satisfactory from a quality microbiology perspective and recommended approval. .

On 6/1/2011 all manufacturing facilities were found acceptable and continue to be acceptable as of the date of this review. EER is attached below.

The applicant has not demonstrated equivalence between the clinical device and the proposed commercial device regarding delivery of the inhalation solution. See the CDRH Consult entered in DARRTS on 6/14/2011 for the list of pending device issues.

The review team did not address labeling during this review cycle.

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 201820/000	**Sponsor:**	CHIESI PHARMS INC
Org. Code:	520		9605 MEDICAL CENTER DR STE 380
Priority:	5		ROCKVILLE, MD 20850
Stamp Date:	25-OCT-2010	**Brand Name:**	TOBRAMYCIN
PDUFA Date:	25-AUG-2011	**Estab. Name:**	
Action Goal:		**Generic Name:**	
District Goal:	26-JUN-2011	**Product Number; Dosage Form; Ingredient; Strengths**	001; SOLUTION; TOBRAMYCIN; 300MG

FDA Contacts:	A. CUFF	Project Manager	(HF-01)	301-796-4061
	S. PAGAY	Review Chemist		301-796-1429
	R. MADURAWE	Team Leader		301-796-1408

Overall Recommendation: ACCEPTABLE on 01-JUN-2011 by M. STOCK (HFD-320) 301-796-4753

Establishment: **CFN:** 1419377 **FEI:** 1419377

CATALENT PHARMA SOLUTIONS (FMLY CARDINAL HEALTH)
2200 LAKE SHORE DRIVE

WOODSTOCK, IL 60098

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE LABELER

FINISHED DOSAGE MANUFACTURER

FINISHED DOSAGE PACKAGER

Profile: AEROSOL DISPERSED MEDICATION **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 15-NOV-2010

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: **CFN:** 1055327 **FEI:** 1000110912

CATALENT PHARMA SOLUTIONS LLC
(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE RELEASE TESTER

FINISHED DOSAGE RELEASE TESTER

FINISHED DOSAGE STABILITY TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 10-NOV-2010

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment:	**CFN:** (b) (4)	**FEI:** (b) (4)	
	(b) (4)		
DMF No:		**AADA:**	
Responsibilities:			
Profile:		**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	01-JUN-2011		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Establishment:	**CFN:** (b) (4)	**FEI:** (b) (4)	
	(b) (4)		
DMF No:		**AADA:**	
Responsibilities:			
Profile:		**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	14-FEB-2011		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

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/s/

SHRIKANT N PAGAY
08/24/2011

RAPTI D MADURAWE
08/24/2011

NDA 201-820
Tobramycin Inhalation Solution

Chiesi Pharmaceuticals, Inc.
Shrikant Pagay
Chemistry Reviewer
Office of New Drug Quality Assessment

Table of Contents

Chemistry Review Data Sheet

1. NDA or ANDA 201-820

2. REVIEW #: 1

3. REVIEW DATE: 3/1/2011

4. REVIEWER: Shrikant Pagay

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	10/26/2010
Amendment	11/15/2010
Amendment	12/2/2010
Amendment	12/6/2010
Amendment	12/20/2010
Amendment	1/21/2011
Amendment	2/25/2011
Amendment	5/13/2011
Amendment	5/13/2011
Amendment	6/10/2011

7. NAME & ADDRESS OF APPLICANT:

Name:	Chiesi Pharmaceuticals Inc.
Address:	9605 medical Center Drive Suite 380 Rockville, MD 20850
Representative:	Erika Panico

Chemistry Review Data Sheet

Telephone: 301-424-2661

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Pending approval
b) Non-Proprietary Name (USAN): Tobramycin
c) Code Name/# (ONDC only): CHF1538
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b) (2)

10. PHARMACOL. CATEGORY: Anti infective

11. DOSAGE FORM: Inhalation Solution

12. STRENGTH/POTENCY: 300 mg/4 mL

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: _X__Rx ___OTC

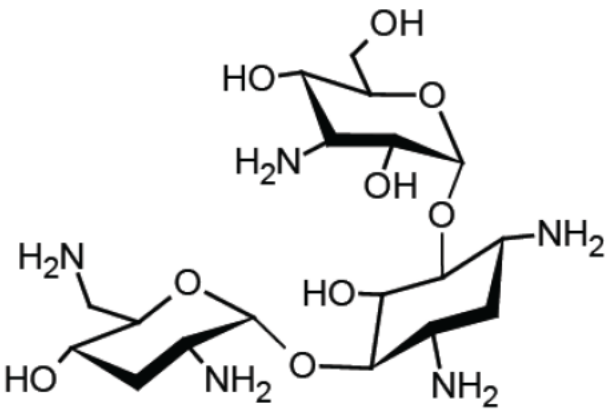
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

____X__Not a SPOTS product

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

O-3-Amino-3-deoxy-α-D-glucopyranosyl-(1→6)-O-[2,6-diamino-2,3,6-trideoxy-α-D-ribo hexopyranosyl-(1→4)]-2-deoxy-D-streptamine



Molecular Formula: $C_{18}H_{37}N_5O_9$

Relative Molecular Mass: 467.52

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Tobramycin (b) (4)	1	Adequate	S. Pagay (6/24/2011)	
	III		(b) (4)	4			
	III			4			
	III			4			

[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:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	72,068	
NDA	50,753	RLD

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	Acceptable	6/1/2011	M. Stock
Pharm/Tox	NA		

Biopharm	NA		
LNC	NA		
Methods Validation	NA		
DMEPA	Pending		
EA	NA		
Microbiology	Pending		R. Mello
CDRH	Pending		S. De; consult through Clinical

19. ORDER OF REVIEW (OGD Only): NA

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for NDA 201-820

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product. An "Acceptable" site recommendation from the Office of Compliance has been made. This application is recommended for approval from the CMC perspective pending satisfactory resolution of the device bridging studies (CDRH), the quality microbiology evaluation, and the labeling negotiations.

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

NA

II. Summary of Chemistry Assessments

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

Drug Substance:
Tobramycin is an aminoglycoside antibiotic which exhibits bactericidal activity against a broad spectrum of bacteria. It inhibits bacterial protein synthesis. The drug substance is (b) (4) . It is supplied as a (b) (4) . Tobramycin is well characterized for the related substances and degradation products. It is freely soluble in water (b) (4) Tobramycin sulfate has been approved previously in several dosage forms including inhalation solution. Tobramycin is supplied as a (b) (4) drug substance; however, the endotoxin level in the drug substance is controlled. Tobramycin is active against many strains of gram-negative bacteria including *Pseudomonas aeruginosa* which is the primary cause of lung infections in CF patients.

Appropriate quality of the tobramycin drug substance is assured by controls described in (b) (4) , in conjunction with the acceptance specification listed in this NDA.

Drug Product:

Tobramycin inhalation solution is a sterile aqueous solution of tobramycin, sulfuric acid, sodium chloride, sodium hydroxide and water for injection. Sulfuric acid is used to (b) (4) and for adjusting the pH. Sodium hydroxide solution can also be used to adjust the pH. Sodium chloride is used to (b) (4)

[redacted], and water for injection [redacted]. No preservatives are used in the formulation. [redacted] was used throughout the manufacturing process, and the tobramycin solution was prepared [redacted]. The solution was filtered using [redacted]. Appropriate in-process controls are used in the preparation of tobramycin solution, including the [redacted]. The primary container is a clear, low density polyethylene unit dose ampoule. The secondary container is a pre-printed [redacted]; each contains one strip of four unit-dose ampoules. A 28 days treatment package is a box containing 14 over-pouches, corresponding to 56 single-dose containers, and a printed package leaflet. The drug product is stored in refrigerator at 36-46 °F/2-8 °C. When the product is removed for administration, the in-use storage condition is 25°C. The shelf life is 24 months under refrigeration condition and 28 days under room temperature. Sufficient stability data is provided to support the claim for setting the expiration date.

Since tobramycin is highly toxic when given IV, sufficient drug levels in lungs are difficult to achieve without reaching the toxic level. When administered by inhalation, sufficient drug is delivered in lungs with only minimum systemic absorption.

Formulation Differences between this NDA and Reference Listed Drug (RLD)
The proposed pH and osmolality of this formulation is different than for the RLD which is Novartis'Tobi Inhalation Solution, approved in 1997. Osmolality of this formulation is between the osmolality of [redacted] and Tobi. Also the pH is slightly different than for Tobi; however, both drug products are controlled in the acidic pH range. If there are no issues with any adverse events that relate to these differences, then minor differences in osmolality and pH between the NDA formulation and RLD are acceptable.

Drug Delivery Device:
Tobramycin is delivered by inhalation route using a compressor pump and a nebulizer. The proposed device for marketing is different than the ones used during the clinical trial. Since the devices are approved under the Center for Devices (CDRH), comparability of the device combinations is being reviewed by CDRH as a consult. Based on the feedback from the CDRH consultant, the studies performed to characterize the droplet size distribution of the inhalation solution between the clinical versus the proposed devices are insufficient. It is not clear if in-vitro characterization of droplet size distribution without a clinical study with different devices is sufficient to show equivalency of the clinical versus the proposed device.

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

The inhalation solution is delivered for the topical application to lungs as a fine mist through a compressor and nebulizer. The label provides complete instructions for the drug administration through cleaning and reuse for the next dosing.

C. Basis for Approvability or Not-Approval Recommendation

All manufacturing and control facilities are Acceptable to the Office of Compliance. The sponsor has provided satisfactory response to information requests on 1/21/2011 and 5/13/2011. Also, the 24 month stability study update, including the shelf life proposal was received on 6/10/2011, and is satisfactory. Prior to approval, the following must be satisfactorily concluded:

- Demonstration of equivalence between the clinical device and the proposed commercial device regarding delivery of the inhalation solution (CDRH Consult)
- Assessment of sterility assurance (Quality Microbiologist's Review)
- Labeling negotiations (Review Team)

III. Administrative

A. Reviewer's Signature: ESO

Shrikaant N. Pagay

B. Endorsement Block

Chemist: Shrikant Pagay
CMC-Lead: Stephen Miller

C. CC Block

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/s/

SHRIKANT N PAGAY
06/24/2011

STEPHEN P MILLER
06/24/2011
I concur - this application is recommended for approval from the CMC perspective pending satisfactory resolution of device bridging studies, quality microbiology evaluation, and labeling.