CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201688s000

CHEMISTRY REVIEW(S)

REVIEW #2

From: Mark R. Seggel, Review Chemist

To: NDA 201688 File

Through: Rapti Madurawe, Ph.D., Branch Chief

Date: 21-MAR-2013

Re: NDA 201-688 TOBI Podhaler (tobramycin inhalation powder); Novartis Pharmaceuticals

RECOMMENDATION: As amended, NDA 201688 is recommended for Approval from the chemistry, manufacturing and controls perspective.

Background Information and Basis for Recommendation:

A Complete Response Letter was issued on 19-OCT-2012 for this application. Deficiencies at the (b) (4) manufacturing facility, (b) (4) were noted. All other manufacturing facilities had acceptable cGMP status at the time of the action. See the Chemist's Memo to the application file dated 18-OCT-2012 for additional details.

A Resubmission - Complete Response was submitted by Novartis on 27-NOV-2012. The applicant stated that they believed (b) (4) submission dated (b) (4) fully addressed the deficiencies noted at (b) (4) manufacturing facility.

An update of the cGMP status of all facilities, including (b) (4) was requested through the Establishment Evaluation System (EES) on 05-DEC-2012. All facilities except for (b) (4), Novartis San Carlos and (b) (4) were found acceptable based on prior recommendations.

The CDRH Office of Compliance determined the response from (b) (4) was adequate (see 28-FEB-2013 memo from David Dar) and re-inspection of (b) (4) was not necessary.

Inspection of the Novartis San Carlos drug product manufacturing facility was assigned although the facility had been the subject of a pre-approval inspection in September 2012. While a FDA Form 483 was issued at the end of the inspection, the District Office issued an Acceptable recommendation on 27-SEP-2012. Subsequently, it was determined that re-inspection of San Carlos was not necessary (see attached EES report).

Because the 06-AUG-2012 EER Re-evaluation date had passed, it was determined that inspection of drug substance manufacturer [redacted] (b) (4) was necessary. ([redacted] (b) (4) had been found acceptable on 18-JAN-2012 based on profile.) An inspection was scheduled for [redacted] (b) (4)

In order to expedite approval of the application, Novartis withdrew [redacted] (b) (4) as a tobramycin drug substance manufacturer from the application (18-MAR-2013 amendment, eCTD 0034). Novartis will rely on [redacted] (b) (4) as the sole source of tobramycin for Tobi Podhaler. Novartis provided a written commitment that, "upon NDA approval, [they] will not market batches of TOBI Podhaler in the US using drug substance from this manufacturer [redacted] (b) (4) until such time that [they] file an appropriate post-approval supplement to re-add the manufacturer to the NDA." Note that tobramycin supplied by [redacted] (b) (4) can continue to be used in the manufacture of Novartis' Tobi (tobramycin inhalation solution), a product approved under NDA 50-753 for the same indication.

The EES request for [redacted] (b) (4) was cancelled on 19-MAR-2013. The Office of Compliance issued an Overall Recommendation of Acceptable on 20-MAR-2013 (see attached EES report).

Note that the specifications for [redacted] (b) (4) and [redacted] (b) (4) tobramycin APIs are comparable [redacted] (b) (4) see Section S.4.1, Drug Substance Specification, Chemistry Review #1). In addition, [redacted] (b) (4) in the drug product manufacturing process. Therefore, for all practical purposes, [redacted] (b) (4) and [redacted] (b) (4) [redacted] drug substances are indistinguishable. Both [redacted] (b) (4) and [redacted] (b) (4) APIs were used in the manufacture of clinical trial batches (see file "pharm-dev-clinical] in NDA section 3.2.P.2, Pharmaceutical Development). Finally, [redacted] (b) (4) API was used in the manufacture of two of three primary stability batches.

Labeling negotiations have been completed. In the latest amendment (0034) the carton labeling was revised to remove [redacted] (b) (4) as a country of origin of the drug substance to reflect the CMC amendment: text change from [redacted] (b) (4)" to "*Product of Hungary*". The package insert, blister label, carton labels, and Podhaler device label, as documented in eCTD submissions 0032, 0033 and 0034, are acceptable from the CMC perspective.

####

Attachment 1. EES Report

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application:	NDA 201688/000	**Action Goal:**	
Stamp Date:	21-DEC-2011	**District Goal:**	28-MAR-2013
Regulatory:	27-MAY-2013		
Applicant:	NOVARTIS PHARMS 1 HEALTH PLAZA BLDG 405 2006 EAST HANOVER, NJ 079361080	**Brand Name:** **Estab. Name:** **Generic Name:**	TOBI Podhaler (tobramycin inhalation pow
Priority:	3	**Product Number; Dosage Form; Ingredient; Strengths**	
Org. Code:	520	001; CAPSULE; TOBRAMYCIN; 28MG	

Application Comment:

FDA Contacts:	A. CUFF	Project Manager	(HF-01)	3017964061
	M. SEGGEL	Review Chemist		3017961455
	D. MATECKA	Team Leader		3017961415

Overall Recommendation:	ACCEPTABLE	on 20-MAR-2013	by M. HEAYN	(HFD-320)	3017964753
	PENDING	on 05-DEC-2012	by EES_PROD		
	PENDING	on 05-DEC-2012	by EES_PROD		
	WITHHOLD	on 18-OCT-2012	by S. HERTZ	(HFD-320)	3017963203
	PENDING	on 05-OCT-2012	by EES_PROD		
	PENDING	on 22-JUN-2012	by EES_PROD		
	PENDING	on 17-JAN-2012	by EES_PROD		
	PENDING	on 17-JAN-2012	by EES_PROD		
	PENDING	on 17-JAN-2012	by EES_PROD		

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Establishment Comment: QUALITY CONTROL TESTING EXCLUDING MICROBIAL TESTING. (on 11-JAN-2012 by A. CUFF (HF-01) 3017964061)

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

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				**Reason**	
SUBMITTED TO OC	17-JAN-2012				CUFFA
OC RECOMMENDATION	18-JAN-2012			ACCEPTABLE	SMITHDE
				BASED ON PROFILE	
SUBMITTED TO OC	05-DEC-2012				CUFFA
OC RECOMMENDATION	06-DEC-2012			ACCEPTABLE	STOCKM
				BASED ON PROFILE	

Reference ID: 3280494

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE OTHER TESTER

FINISHED DOSAGE STABILITY TESTER

Establishment Comment: QUALITY CONTROL AND STABILITY TESTING FOR DRUG PRODUCT (on 11-JAN-2012 by A. CUFF (HF-01) 3017964061)

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

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				**Reason**	
SUBMITTED TO OC	17-JAN-2012				CUFFA
SUBMITTED TO DO	18-JAN-2012	10-Day Letter			SMITHDE
DO RECOMMENDATION	12-FEB-2012			ACCEPTABLE	BRYKMANR
LAST FDA INSPECTION IN (b) (4) COVERED THE SAME PROFILE, WITH A FINAL CLASSIFICATION (b) (4)) OF NAI.				BASED ON FILE REVIEW	
OC RECOMMENDATION	13-FEB-2012			ACCEPTABLE	INYARDA
				DISTRICT RECOMMENDATION	
SUBMITTED TO OC	05-DEC-2012				CUFFA
OC RECOMMENDATION	06-DEC-2012			ACCEPTABLE	STOCKM
				BASED ON PROFILE	

Reference ID: 3280494

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE MANUFACTURER

Establishment Comment: DEVICE SITE MANUFACTURER (on 22-JUN-2012 by A. CUFF (HF-01) 3017964061)

Profile: DEVICE KIT ASSEMBLER **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				**Reason**	
SUBMITTED TO OC	22-JUN-2012				CUFFA
SUBMITTED TO DO	22-JUN-2012	Product Specific			INYARDA
SEE EESQUESTIONS EMAIL DATED 6/21/12 FOR THIS NDA					
ASSIGNED INSPECTION TO IB	23-JUN-2012	Product Specific			PHILPYE
DEVICE INVESTIGATOR REQUIRED					
SUBMITTED TO DO	26-JUN-2012	Product Specific			INYARDA
ASSIGNED INSPECTION TO IB	30-JUN-2012	Product Specific			PHILPYE
INSPECTION PERFORMED	(b) (4)		(b) (4)		IRIVERA
INSPECTION SCHEDULED	(b) (4)		(b) (4)		IRIVERA
OC RECOMMENDATION	18-OCT-2012			WITHHOLD	HERTZST
RECOMMENDATION PROVIDED BY CDRH/OC. AN INTER-CENTER CONSULT WAS INITIATED ON 10/5/12 TO PERFORM A QUALITY SYSTEM REVIEW OF THE OBSERVATIONS FOUND ON INSPECTION, THE FIRM¿S RESPONSE, AND THE EIR. CDRH/OC RECOMMENDATION IS TO CLASSIFY THE INSPECTION AS (b) (4) OF THE PENDING NDA, PER REVIEW MEMORANDUM DATED (b) (4).				DISTRICT RECOMMENDATION	
SUBMITTED TO OC	05-DEC-2012				CUFFA
SUBMITTED TO DO	07-DEC-2012	Product Specific			STOCKM
PLEASE NOTE THAT THIS IS A DEVICE MANUFACTURING SITE FOR THE NDA. IF AN INSPECTION IS DONE, PLEASE SEND A DEVICE SPECIALIST.					
ASSIGNED INSPECTION TO IB	07-DEC-2012	Product Specific			PHILPYE
DO RECOMMENDATION	18-MAR-2013			ACCEPTABLE	PHILPYE
PER EMAIL FROM S. HERTZ, 3/18/13, WITH AC MEMO FROM CDRH				BASED ON FILE REVIEW	
OC RECOMMENDATION	19-MAR-2013			ACCEPTABLE	HERTZST
RECOMMENDATION PROVIDED BY CDRH/OC. CDRH/OC PROVIDED A REVIEW OF FIRM¿S RESPONSE TO (b) (4) DEFICIENCY LETTER ON (b) (4) AND FOUND THAT THE DEFICIENCIES APPEAR TO BE ADEQUATELY ADDRESSED. CDRH/OC RECOMMENDATION IS TO CLASSIFY THIS SITE AS ACCEPTABLE.				DISTRICT RECOMMENDATION	

Reference ID: 3280494

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE PACKAGER

Establishment Comment: PACKAGING FOR DRUG PRODUCT (on 11-JAN-2012 by A. CUFF (HF-01) 3017964061)

Profile: CAPSULES, PROMPT RELEASE **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				**Reason**	
SUBMITTED TO OC	17-JAN-2012				CUFFA
SUBMITTED TO DO	18-JAN-2012	10-Day Letter			SMITHDE
PLEASE CHECK TO SEE IF THE CURRENT PROFILE IN FACTS IS INCORRECT - PER CMS THIS FIRMS SEEMS LIKE A PACKAGER OF SOLID ORAL DOSAGE AND NOT ADM - ADM MAY COME FROM INTENDED USE OF PRODUCT AS CAPSULES ARE INSERTED INTO AN INHALATION DEVICE - SITE APPEARS TO BE PACKAGING THE CAPSULES.					
DO RECOMMENDATION	21-JAN-2012			ACCEPTABLE	PHILPYE
FIRM PACKAGES CAPSULES INTO BLISTERS FOR MULTIPLE FINAL PACKAGES - PROFILED INCORRECTLY IN FACTS- AC				BASED ON FILE REVIEW	
OC RECOMMENDATION	22-JAN-2012			ACCEPTABLE	SMITHDE
				BASED ON PROFILE	
SUBMITTED TO OC	05-DEC-2012				CUFFA
SUBMITTED TO DO	07-DEC-2012	Product Specific			SHARPT
DO RECOMMENDATION	29-JAN-2013			ACCEPTABLE	PHILPYE
SEE PREVIOUS DO REC - PACKAGING ONLY.				BASED ON FILE REVIEW	
OC RECOMMENDATION	29-JAN-2013			ACCEPTABLE	SMITHDE
				DISTRICT RECOMMENDATION	

Reference ID: 3280494

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Establishment Comment: MICROBIAL QUALITY CONTROL TESTING (on 11-JAN-2012 by A. CUFF (HF-01) 3017964061)

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

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				**Reason**	
SUBMITTED TO OC	17-JAN-2012				CUFFA
OC RECOMMENDATION	18-JAN-2012			ACCEPTABLE	SMITHDE
				BASED ON PROFILE	
SUBMITTED TO OC	05-DEC-2012				CUFFA
OC RECOMMENDATION	06-DEC-2012			ACCEPTABLE	STOCKM
				BASED ON PROFILE	

Reference ID: 3280494

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** **FEI:** 3007886374

NOVARTIS

150 INDUSTRIAL RD
SAN CARLOS, CA 940706256

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE MANUFACTURER

FINISHED DOSAGE OTHER TESTER

FINISHED DOSAGE STABILITY TESTER

Establishment Comment: PROFILE CHANGED FROM CHG TO ADM BASED ON RECOMMENDATION OF DGMPA FACILITY REVIEWER AND CONCURRENCE FROM NDMAB BRANCH CHIEF. SITE IS MANUFACTURING CAPSULES WITH A SPRAY-DRIED DISPERSION THAT IS INTENDED FOR INHALATION THROUGH A PODHALER. WHILE CHG COVERS THE CAPSULES PART OF THE PROCESS, IT DOES NOT CAPTURE THE COMPLEXITY OF THE CAPSULE FOR INHALATION. (on 10-MAY-2012 by D. SMITH (HFD-323) 3017965321)

PRODUCT DEVELOPMENT AND MANUFACTURING INCLUDE ELEMENTS OF QBD. PQM MEMO WILL BE FILED IN DARRTS. IT MAY BE USEFUL TO HAVE CMC REVIEWER PARTICIPATE IN INSPECTION. (on 07-MAR-2012 by M. SEGGEL () 3017961455)

MANUFACTURING, QUALITY CONTROL AND STABILITY TESTING FOR DRUG PRODUCT (on 11-JAN-2012 by A. CUFF (HF-01) 3017964061)

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

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				**Reason**	
SUBMITTED TO OC	17-JAN-2012				CUFFA
SUBMITTED TO DO	18-JAN-2012	Product Specific			SMITHDE
ASSIGNED INSPECTION TO IB	24-JAN-2012	Product Specific			WMILLAR
INSPECTION SCHEDULED	24-AUG-2012				WMILLAR
INSPECTION PERFORMED	27-SEP-2012		27-SEP-2012		LDESOUZA
THE FORM FDA 483 WAS ISSUED ON 9/27/12. THE OBSERVATIONS PERTAINING TO THE DRUG CGMPS APPEAR TO BE VAI IN NATURE. SEVERAL CORRECTIVE ACTIONS WERE INITIATED/COMPLETED PRIOR TO THE CLOSE OUT MEETING. THE FIRM PLANS TO RESPOND IN WRITING TO EACH OBSERVATION WITHIN 15 CALENDAR DAYS. OVERALL, SAN-DO PLANS TO RECOMMEND ¿ACCEPTABLE¿ FOR THE DRUG PORTION OF THE NDA.					
DO RECOMMENDATION	27-SEP-2012			ACCEPTABLE	LDESOUZA
THE FORM FDA 483 WAS ISSUED ON 9/27/12. THE OBSERVATIONS PERTAINING TO THE DRUG CGMPS APPEAR TO BE VAI IN NATURE. SEVERAL CORRECTIVE ACTIONS WERE INITIATED/COMPLETED PRIOR TO THE CLOSE OUT MEETING. THE FIRM PLANS TO RESPOND IN WRITING TO EACH OBSERVATION WITHIN 15 CALENDAR DAYS. OVERALL, SAN-DO PLANS TO RECOMMEND ¿ACCEPTABLE¿ FOR THE DRUG PORTION OF THE NDA.				INSPECTION	
OC RECOMMENDATION	11-OCT-2012			ACCEPTABLE	SAFAAIJAZIR
				DISTRICT RECOMMENDATION	
SUBMITTED TO OC	05-DEC-2012				CUFFA
SUBMITTED TO DO	06-DEC-2012	10-Day Letter			STOCKM
PAI ALREADY PERFORMED; NDA HAS BEEN SENT THROUGH FOR ANOTHER REVIEW CYCLE.					
ASSIGNED INSPECTION TO IB	18-JAN-2013	Product Specific			LDESOUZA
DO RECOMMENDATION	14-MAR-2013			ACCEPTABLE	LDESOUZA
PER FIRM'S RESPONSE TO 483 DATED 10/12/12, AND DISCUSSION WITH SCSO INOKON ON 3/13/13, ALL CORRECTIVE ACTIONS STEMMING FROM THE 9/12-27/12 PAI INSPECTION FOR NDA 201688 APPEARED ADEQUATE. SAN-DO RECOMMENDS ACCEPTABLE.				ADEQUATE FIRM RESPONSE	

OC RECOMMENDATION	18-MAR-2013	ACCEPTABLE	SAFAAIJAZIR
		DISTRICT RECOMMENDATION	

APPEARS THIS WAY ON ORIGINAL

Reference ID: 3280494

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** 9611204 **FEI:** 3007303963

NOVARTIS PHARMA AG

LICHTSRASSE 35
BASEL, , SWITZERLAND

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Establishment Comment: QUALITY CONTROL TESTING (EXCLUDING EP SPECIFIC TEST) INCLUDING MICROBIAL TESTING (on 11-JAN-2012 by A. CUFF (HF-01) 3017964061)

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

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				**Reason**	
SUBMITTED TO OC	17-JAN-2012				CUFFA
SUBMITTED TO DO	18-JAN-2012	GMP Inspection			SMITHDE
ASSIGNED INSPECTION TO IB	21-JAN-2012	GMP Inspection			PHILPYE
INSPECTION SCHEDULED	30-MAY-2012		19-JUL-2012		PHILPYE
DO RECOMMENDATION	17-OCT-2012			ACCEPTABLE	PHILPYE
				INSPECTION	
OC RECOMMENDATION	17-OCT-2012			ACCEPTABLE	SMITHDE
				DISTRICT RECOMMENDATION	
SUBMITTED TO OC	05-DEC-2012				CUFFA
OC RECOMMENDATION	06-DEC-2012			ACCEPTABLE	STOCKM
				BASED ON PROFILE	

Reference ID: 3280494

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** 2416082 **FEI:** 2416082

NOVARTIS PHARMACEUTICALS CORP

OLD MILL RD
SUFFERN, NY 10901

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE OTHER TESTER

FINISHED DOSAGE OTHER TESTER

FINISHED DOSAGE STABILITY TESTER

Establishment Comment: QUALITY CONTROL TESTING (EXCLUDING EP SPECIFIC TEST) INCLUDING MICROBIAL TESTING (on 11-JAN-2012 by A. CUFF (HF-01) 3017964061)

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

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				**Reason**	
SUBMITTED TO OC	17-JAN-2012				CUFFA
OC RECOMMENDATION	18-JAN-2012			ACCEPTABLE	SMITHDE
				BASED ON PROFILE	
SUBMITTED TO OC	05-DEC-2012				CUFFA
OC RECOMMENDATION	06-DEC-2012			ACCEPTABLE	STOCKM
				BASED ON PROFILE	

Reference ID: 3280494

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE OTHER TESTER

FINISHED DOSAGE STABILITY TESTER

Establishment Comment: MICROBIOLOGICAL TESTING - QUALITY CONTROL AND STABILITY TESTING (on 11-JAN-2012 by A. CUFF (HF-01) 3017964061)

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

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				**Reason**	
SUBMITTED TO OC	17-JAN-2012				CUFFA
SUBMITTED TO DO	18-JAN-2012	10-Day Letter			SMITHDE
DO RECOMMENDATION	20-JAN-2012			ACCEPTABLE	MFADDEN
A CGMP INSPECTION CONDUCTED (b) (4) FOCUSED ON THE LABORATORY AND QUALITY SYSTEMS. NO FDA 483 WAS ISSUED. SEVERAL VERBAL OBSERVATIONS WERE DISCUSSED AND CORRECTED PRIOR TO THE CLOSE OUT. METHOD VALIDATION AND METHOD TRANSFER WERE COMPLETED. (b) (4) RECOMMENDS THIS FIRM AS ACCEPTABLE.				BASED ON FILE REVIEW	
OC RECOMMENDATION	22-JAN-2012			ACCEPTABLE	SMITHDE
				DISTRICT RECOMMENDATION	
SUBMITTED TO OC	05-DEC-2012				CUFFA
OC RECOMMENDATION	06-DEC-2012			ACCEPTABLE	STOCKM
				BASED ON PROFILE	

Reference ID: 3280494

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE OTHER TESTER

Establishment Comment: IN-PROCESS CONTROL TESTING FOR DRUG PRODUCT (on 11-JAN-2012 by A. CUFF (HF-01) 3017964061)

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

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				**Reason**	
SUBMITTED TO OC	17-JAN-2012				CUFFA
OC RECOMMENDATION	18-JAN-2012			ACCEPTABLE	SMITHDE
				BASED ON PROFILE	
SUBMITTED TO OC	05-DEC-2012				CUFFA
OC RECOMMENDATION	30-JAN-2013			ACCEPTABLE	SHARPT
				BASED ON PROFILE	

Reference ID: 3280494

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

DMF No: (b) (4) **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER

DRUG SUBSTANCE STABILITY TESTER

Establishment Comment: MANUFACTUING, QUALITY CONTROL AND STABILITY TESTING FOR DRUG SUBSTANCE (on 11-JAN-2012 by A. CUFF (HF-01) 3017964061)

Profile: (b) (4) **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	17-JAN-2012				CUFFA
OC RECOMMENDATION	18-JAN-2012			ACCEPTABLE	SMITHDE
				BASED ON PROFILE	
SUBMITTED TO OC	05-DEC-2012				CUFFA
OC RECOMMENDATION	06-DEC-2012			ACCEPTABLE	STOCKM
				BASED ON PROFILE	

Reference ID: 3280494

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/s/

MARK R SEGGEL
03/21/2013

RAPTI D MADURAWE
03/21/2013

NDA EIR REVIEW MEMORANDUM

DATE: October 17, 2012

FROM: Consumer Safety Officer, Radiology, Anesthesiology, and Neurology Devices Branch (RANDB), Division of Enforcement B (DOE B), Office of Compliance (OC), Center for Devices and Radiological Health (CDRH)

THROUGH: Medical Device Quality System Specialist, Office of Compliance, CDRH

Chief, RANDB, DOE B, OC, CDRH 10-17-2012

TO: Senior Policy Advisor, Division of Good Manufacturing Practice Assessment (DMPQ), Office of Manufacturing and Product Quality (OMPQ), Office of Compliance, Center for Drug Evaluation and Research (CDER)

SUBJECT: Review of New Drug Application (NDA) Preapproval Establishment Inspection Report (EIR), FDA 483, Exhibits, and Firm's Response

Applicant: Novartis Pharmaceuticals Corporation
150 Industrial Rd
San Carlos, CA 94070

FEI: 3007886374

Inspection Site: (b) (4)

FEI: (b) (4)

NDA: **201688**

Reference ID: 3286837

PRODUCT:	Tobi Podhaler
ORA RECOMMENDATION:	VAI
INVESTIGATOR:	Francis J. Eng, SAN-DO
SITE COMPLIANCE DECISION:	OAI – Withhold
CDRH RECOMMENDATION:	Nonapprovable – OAI Inspection

I. Purpose and Type of Inspection

The purpose for the inspection was a premarket approval inspection to approve the above facility for a New Drug Application (NDA).

The current inspection was a comprehensive baseline Level 2 inspection.

II. Background Information

Novartis submitted an NDA for Tobi Podhaler, a dry powder form of tobramycin for treating chronic P. aeruginosa lung infection in cystic fibrosis patients over six years. The Tobi Podhaler is a combination drug/device product with drug precedence. The product consists of an inhalation device, which is manufactured by [redacted] (b) (4) and a drug capsule. [redacted] (b) (4) was included in the pre-approval inspection plan for the NDA and CDER requested that CDRH review the EIR.

III. Regulatory History

- **NDA Inspection Site 1: Novartis Pharmaceuticals Corporation (manufacturer)**

150 Industrial Rd
San Carlos, CA 94070

FEI: 3007886374

09/17/2012 – 09/27/2012	An inspection was conducted by SAN-DO and has yet to be classified. This inspection was a pre-approval PDUFA inspection for the Tobi Podhaler.

Reference ID: 3286837

08/25/2005 – 01/19/2006	An inspection was conducted by SAN-DO and was classified as NAI. This inspection was a pre-approval PDUFA inspection for the Insulin Inhalation Powder.

- **NDA Inspection Site 2:** (b) (4) (b) (4) **(contract manufacturer)**

(b) (4) FEI: (b) (4)

This is the initial inspection of this manufacturing facility.

IV. Current Inspection

The Radiology, Anesthesiology, and Neurology Devices Branch of the Division of Enforcement B has completed its good manufacturing practices review and evaluation under the Quality System regulation of the Establishment Inspection Report (EIR) and exhibits for the inspection which closed on (b) (4) and the firm's response dated (b) (4) which took place at (b) (4) (b) (4) facility. The inspection of this firm indicates that it meets the criteria of a Situation I, in Compliance Program, CP 7383.001, Part V, dated March 5, 2012, in that one or more major deficiencies of the firm's quality system have resulted in the inspection being classified OAI.

The OAI level was reached because there was a deficiency in one or more subsystems of the firm's quality system, for example, production and process controls.

CDRH does not concur with the classification recommendation and is requesting that the inspection be classified as OAI, as the firm failed to adequately control environmental conditions of its clean room.

V. Quality System Review

The review of the EIR, exhibits, FDA 483, and the firm's response follows below. The QS regulation violations appear in a descending order of significance.

Reference ID: 3286837

- **21 CFR 820.70(c)**

Failure to establish and maintain adequate procedures to control environmental conditions that could reasonably be expected to have an adverse effect on product quality, and failure to periodically inspect environmental control systems to verify that the system is adequate and funtioning properly, as required by 21 CFR 820.70(c). For example:

1. (b) (4)

2.

3.

This cite is supported by Observation 1 and 2 of the FDA 483, pages 13 – 15 of the EIR, and Exhibit Nos. 25 and 28.

The response dated (b) (4) is not adequate. The firm did not provide documentation, or a plan, which includes requirements to (b) (4) . The firm notes that it will develop specifications for (b) (4) however, the firm failed to provide documentation of its respective protocol and evidence of its implementation. The firm states that it will revise its (b) (4) procedure to clearly list the two media to use, and train its employees on the revised procedure. The firm failed to provide documentation of the procedure and evidence of its implementation, specifically documentation of (b) (4)

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VI. Observations Pertaining To Other Regulations

There are no observations pertaining to other regulations.

VII. Nonsupportable FDA 483 Observations

There are no nonsupportable FDA 483 observations.

VIII. CDRH Recommendation and Follow-up

CDRH has classified the inspection OAI based on the EIR dated (b) (4) (b) (4) CDRH recommends withholding approval of the pending NDA for the Tobi Podhaler.

David Dar

David Dar

Reference ID: 3286837

Drafted: DDar: 10/16/12
Reviewed/revised: QSTeamMember: ESmith: 10/17/12
Reviewed/approved: ABranchChief: [MM/DD/YY] T. Arthur 10/17/2012
Final: VA Murray: 10/17/12

cc:

WO66-3523	OC/DOE B Chron File
WO66-3521	OC/FOB/PMA Program Coordinator
HFR-PA1530	F. Eng, Investigator, SAN-DO

CTS: ICC1200183

Reference ID: 3286837

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

/s/

SHANNON J CREWS
04/02/2013

NDA 201-688

TOBI Podhaler™
(tobramycin inhalation powder)
28 mg / capsule

Novartis Pharmaceuticals Corporation

Mark R. Seggel

ONDQA
Division of New Drug Quality Assessment II
Branch V

for the Division of Anti-Infective Products

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Chemistry Review Data Sheet

1. NDA 201-688

2. REVIEW #: 1

3. REVIEW DATE: 09-SEP-2012

4. REVIEWER: Mark R. Seggel

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Not Applicable	-

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed (eCTD)	Document Date
Original NDA (0001)	21-DEC-2011
Quality/Response to Information Request (0003)	24-FEB-2012
Quality/Response to Information Request (0008)	21-MAY-2012
Quality/Response to Information Request (0009)	31-MAY-2012
Quality/Response to Information Request (0010)	08-JUN-2012
Amendment [corrected Section P.2] (0011)	28-JUN-2012
Quality/Response to Information Request (0020)	30-AUG-2012

7. NAME & ADDRESS OF APPLICANT:

Name:	Novartis Pharmaceuticals Corporation
Address:	One Health Plaza East Hanover, NJ 07936-1080
Representative(s):	John Noh, Pharm.D.
Telephone:	862-778-1689

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: TOBI Podhaler™
   b) Non-Proprietary Name (USAN): Tobramycin
   c) Code Name/#: TIP; TBM100C
   d) CAS Registry Number: *32986-56-4*
   e) Chem. Type/Submission Priority:
      i. Chem. Type: 3
      ii. Submission Priority: S

Reference ID: 3187826

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

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

11. DOSAGE FORM: Inhalation Powder

12. STRENGTH/POTENCY: 28 mg / capsule

13. ROUTE OF ADMINISTRATION: Inhalation

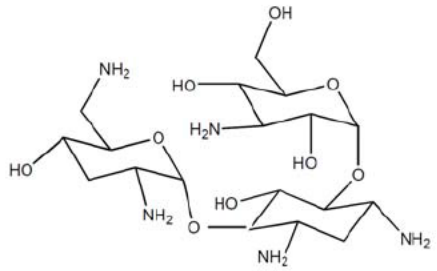
14. Rx/OTC DISPENSED: _X_Rx ___OTC

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

USAN: (1) D-Streptamine, *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-;
(2) *O*-3-Amino-3-deoxy-α-D-glucopyranosyl-(1→4)-*O*-[2,6-diamino-2,3,6-trideoxy-α-D-*ribo*-hexopyranosyl-(1→6)]-2-deoxy-Lstreptamine.

Structural Formula:



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

Molecular Weight: 467.51

Reference ID: 3187826

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	3	Adequate	R.Samy, OGD, 06/12/12	same API used in N50753
	II		Tobramycin	1	Adequate	M. Seggel 09/09/12	same API used in N50753
	II		DSPC	1	Adequate	Ravi Kasliwal 01/02/02 11/10/03 M. Seggel 09/09/12	
	IV		DSPC	3	Adequate	M. Salazar-Driver 02/16/12	
	IV		Hypromellose capsules	1	Adequate	M. Seggel 09/09/12	
	III		(b) (4)	1	Adequate	M. Seggel 09/09/12	
	III			1	Adequate	M. Seggel 09/09/12	
	III		T-326 DPI Device	1	Adequate	M. Seggel 09/09/12	See also CDRH ODE consult review for N201-688: concerns with usability

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
IND 64,409	Tobramycin Inhalation Powder	Pre-IND 64409 submitted by Chiron in 2002; Chiron acquired by Novartis 2006.
NDA 50-753	Tobramycin Inhalation Solution	PathoGenesis NDA AP 1997; acquired 2001 by Chiron; acquired by Novartis 2006.

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not applicable		
EES		*pending*	
Pharm/Tox	Approval recommended. Excipients qualified; DSPC-degradant S-lyso-PC qualified at proposed level.	30-JUL-2012	A. Ellis, DAIP

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Clinical Pharmacology	Approval	20-AUG-2012	R.P. Owen, OCP
ONDQA Biopharmaceutics	Not applicable		
LNC	Not applicable		
Methods Validation	Not applicable		
OSE	Proprietary name acceptable; other labeling recommendations	26-APR-2012	A. Winiarski, DMEPA
Division of Medical Policy Programs	Patient labeling recommendations provided	28-AUG-2012	S. Hutchins, DMPP
EA	Categorical exemption (<1 ppb) acceptable	09-SEP-2012	M. Seggel
Quality Microbiology	Acceptable	06-SEP-2012	S. Langille, NDMS
CDRH ODE/DAGID/ARDB	In-vitro performance, mechanical safety and reliability adequate. Biocompatibility for ISO 10993-1 "externally communicating device" not demonstrated. Deficient from Human Factors perspective.	24-AUG-2012 24-AUG-2012	S. De, CDRH Q.N. Nguyen, CDRH

19. GOAL DATES

PDUFA Goal: 19-OCT-2012

Reference ID: 3187826

The Chemistry Review for NDA 201-688

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA, as amended, has provided sufficient information to assure the identity, strength, quality, purity, and potency of the drug product. The labels have adequate information (e.g., description, how supplied, storage statements) as required.

However, at this time this NDA is not recommended for approval. GMP inspections are outstanding and the Office of Compliance has not issued an overall recommendation at this time.

A CDRH consult of the drug product did not recommend approval of the device from an engineering and human factors perspective. However, from the ONDQA CMC perspective, the device materials of construction, manufacturing, quality control, and performance are acceptable.

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)

Tobramycin inhalation powder (TIP) is indicated for the management of cystic fibrosis patients with *Pseudomonas aeruginosa*. It is a new, dry powder formulation of tobramycin for oral inhalation and is to be administered with the T-326 dry powder inhaler, known as 'Podhaler'. The inhalation powder is formed of low density particles "with favorable aerodynamic characteristics (i.e., suitable for delivery to the lung) and high porosity."

TOBI Podhaler represents a more convenient dosage form compared to the approved tobramycin inhalation solution, 300 mg (TOBI, Novartis NDA 50-753, AP 22-DEC-1997), which requires a nebulizer and an air compressor for drug administration. Compared to TOBI, tobramycin inhalation powder offers a shorter administration time (ca. 6 min.) and room temperature storage.

Tobramycin inhalation powder is supplied as clear, colorless size #2 hydroxypropyl methylcellulose (hypromellose, HPMC) capsules containing tobramycin, USP (28 mg),

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sulfuric acid , NF, to adjust pH [redacted] (b) (4) 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC) [redacted] (b) (4) and calcium chloride [redacted] (b) (4) [redacted] (b) (4), USP. DSPC and calcium chloride have been adequately qualified for use in this inhalation product (see A. Ellis' Pharm/Tox review, 30-JUL-2012). The DSPC degradant S-lyso-phosphocholine has been qualified at proposed limit. Note also that the drug product impurities in tobramycin inhalation powder are controlled to the same levels as in TOBI (tobramycin inhalation solution). A dose, administered twice daily, consists of 4 capsules (112 mg tobramycin).

The low density, porous particles within the desired range for inhalation [redacted] (b) (4)) (referred to as PulmoSpheres®) are manufactured using Novartis' proprietary spray drying technology ('PulmoSphere Technology').

Essentially, a fine oil-in-water emulsion containing tobramycin [redacted] (b) (4) is sprayed dried. [redacted] (b) (4) The finished product is packaged in laminated aluminum-aluminum foil blisters. The product is stored at room temperature, but must be protected from moisture as TIP capsules are hygroscopic.

Throughout the manufacture of Phase III materials (clinical trials C2301 [vs. placebo] and C2302 [vs. TOBI, tobramycin inhalation solution]), the same manufacturing process and conditions were used. To prepare for commercial supply, improvements were made to extend the physical stability of the fine emulsion feedstock. [redacted] (b) (4) Secondly, adjustments were made to the spray-drying process and equipment [redacted] (b) (4) Spray-drying parameters were evaluated using a Quality by Design (QbD) approach.

Dr. Lin Qi, ONDQA Division II QbD Liaison provided significant assistance with assessment of the DoE and QbD elements documented in section 3.2.P.2 Pharmaceutical Development. A Product Quality and Manufacturing memo was prepared for the Office of Compliance to facilitate their preparation for a pre-approval inspection.

The product quality system includes manufacturing under relatively narrow process parameters. A Quality by Design approach was used to evaluate spray-drying process parameters. Design of Experiment studies were undertaken only to establish the parameters for commercial manufacture and improve yields. A formal design space is not being proposed. The additional data provide further linkage of the Phase III and commercial (Improved Process) materials.

In-process tests including [redacted] (b) (4) pH and emulsion droplet size. Tests on the bulk spray-dried powder include

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(b) (4) residual perflubron and particle size. The drug product specification includes tests for identification, assay, degradation products, DSPC-degradant S-lyso-phosphocholine (an impurity reported to induce bronchoconstriction), capsule content uniformity, microbial enumeration, and foreign particulate matter. Appropriate acceptance criteria for each of these tests have been established, and are supported by release and stability data.

Of particular importance to an oral inhalation product are the tests for delivered dose uniformity (emitted dose), aerodynamic particle size distribution (APSD), moisture content and foreign particulate matter. The APSD is measured using a Next Generation Impactor operated at 60 liters per minute for 2 seconds (i.e., 2 L). Based on measured APSD, acceptance criteria were established for particle size ranges >4.46 µm (Group 2, NGI stages 1 + 2), 4.46 to 1.66 µm (Group 3, NGI stages 3 + 4) and < 1.66 µm (Group 4, NGI stages 5 to filter). Note that the cut-off diameters at 60 LPM are 0.15 µm to < 1 µm greater than at 35 LPM. The mean target delivered dose is 102 mg when measured under the same test conditions. It should be noted that the delivered dose at a (b) (4) airflow, which may be more representative of younger or sicker patients, is approximately (b) (4) of the target dose (102 mg), while at 60 LPM, the DD is approximately 100% of the target dose.

T-326 device, or Podhaler, is a breath-activated, pre-metered dry powder inhaler (DPI) (doses are presented in capsules). It was developed by Inhale Therapeutics/Nektar Therapeutics, and is documented in Novartis' DMF (b) (4). From the CMC perspective, DMF (b) (4) is acceptable, as amended. It is constructed of (b) (4) There are no electronic components and an external energy source (e.g., air compressor) is not required. The airflow generated by the patient inhalation disperses the dry powder. Qualification of mucosal membrane and drug contacting components was based on physicochemical testing and biocompatibility testing. Biocompatibility testing was demonstrated in accordance with ISO 10993 and USP <88>. This testing is sufficient from a CMC perspective.

Tobramycin, the active ingredient in TOBI Podhaler, is an aminoglycoside antibiotic produced by (b) (4) *Streptomyces tenebrarius*. It acts primarily by disrupting protein synthesis leading to altered cell membrane permeability, progressive disruption of the cell envelope, and eventual cell death. The same material is used in the manufacture of TOBI (tobramycin inhalation solution) under Novartis' NDA 50-753.

Tobramycin inhalation powder has been approved in Europe and Canada. Colobreathe (colistimethate sodium inhalation powder) uses a similar dry powder inhaler (Turbospin) and was recently approved in Europe.

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

Tobramycin inhalation powder is administered twice daily for 1 month. Each dose consists of four 28-mg capsules. A one-month supply contains 4 kits; each kit includes 56 capsules sufficient for one week and a T-326 dry powder inhaler device. The monthly kit contains a spare T-326 inhaler. The daily dose is provided on a single blister card with 2 rows of four capsules, designated for morning and evening dosing.

Tobramycin inhalation powder is, "administered in alternating period of 28 days, i.e., after 28 days of therapy, patients should stop TIP therapy for the next 28 days, and then resume therapy for the next 28 day on/28 day off cycle"

The drug product is proposed for patients 6 years of age and older. However, it is likely that some pediatric patients, or others who are very sick, will be unable to generate sufficient flow rate to effectively use this product (see clinical reviews).

A 36 months shelf life for TIP, 28 mg, when stored according to the labeling: Store at 25°C (77°F). Excursions permitted to 15-30°C (59-86 °F) [See USP Controlled room Temperature]. Protect from moisture.

C. Basis for Approvability or Not-Approval Recommendation

Tobramycin drug substance is adequately documented in (b) (4) DMF (b) (4) and (b) (4) DMF (b) (4). Tobramycin manufactured by (b) (4) and (b) (4), and meeting the same quality requirements is used in the manufacture of TOBI (tobramycin inhalation solution) as documented in Novartis's approved NDA 50-753.

Overall, the applicant has provided sufficient information on raw material controls, manufacturing processes and process controls, and adequate specifications for assuring consistent product quality of the drug product. 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.
The New Drug Microbiology Staff reviewer has recommended approval of the application from the quality microbiology perspective.

A placebo-controlled study was conducted (C2303) to link the Phase III materials and the commercial product. It should be noted that the formulation, per se, was not changed in the process. While from a clinical efficacy perspective study C2303 was not particularly informative, pharmacokinetic data suggest that the Phase III and commercial materials are equivalent (see Clinical Pharmacology review). And, although there are small differences in particle size as measured on the bulk powder, the critical parameters of emitted dose and aerodynamic particle size distribution are comparable, adequately linking the Phase III product and the commercial product.

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Drug product stability has been established with real time data through 36 months at 25°C/60% RH and/or 30°C/75% RH. However, blisters should not be opened until the dose is to be administered.

Several CMC Comparability Protocols were included in the NDA. Proposed changes include use of an alternate [redacted] (b) (4) to manufacture the T-326 inhaler, use of alternate sources of DSPC, use of alternate suppliers of HPMC capsule shells, addition of an alternate blister packaging site, scale up of drug product manufacturing [redacted] (b) (4) and process improvements [redacted] (b) (4) Revised protocols incorporating minor FDA requested revisions were submitted, and are acceptable.

While device performance (e.g., airflow resistance as a function of flow rate) has been characterized, and reproducible *in vitro* product performance (i.e., emitted dose or delivered dose uniformity, and aerodynamic particle size distribution) has been demonstrated, the ability of some patients, especially the younger (ca. 6 years) pediatric patients, to generate sufficient airflow to achieve adequate dosing remains a concern (see DAIP clinical reviews).

Novartis' DMF [redacted] (b) (4) for the T-326 dry powder inhaler (i.e., Podhaler) was reviewed in part by CDRH ODE / DAGID / ARBD (engineering and human factors / usability perspectives). S. De, CDRH biomedical engineer concluded that the Tobi Podhaler reliably delivers the target delivered dose with a mass-median aerosol diameter (MMAD) between [redacted] (b) (4) over the range of batch formulations studied, and that the mechanical safety and reliability for the proposed device had been adequately demonstrated. However, he also noted that biocompatibility testing may not have been adequate for what he considers an "externally communicating device…due to the potential for chemical leachants from the device entering the patient's airway". Considering this and the issues noted in the CDRH Human Factors Pre-Market Evaluation Team CDRH Human Factors assessment, he does not recommend approval of the device from the device-engineering standpoint.

Consistent with the Pulmonary drug product review team viewpoint, classification of the dry powder inhaler as an "externally communicating" is not warranted. The [redacted] (b) (4) inhaler mouthpiece is in contact with the patient mouth and lips for only a few minutes twice a day. The gas path and [dry] drug product contact surfaces are the same material. Based on a safety assessment on the low levels of extractables observed in controlled extraction studies, Novartis concluded that further leachables testing was not necessary. This assessment is adequately supported. Assessment of extracts per ISO 10993 (cytotoxicity, sensitization, and irritation) and USP <88> (acute systemic toxicity) is routinely considered sufficient for demonstrating biocompatibility of dry powder inhalers and other inhalation devices. The results of these tests on T-326 components were negative. Therefore, from the CMC perspective the device has been adequately characterized and is suitable for the intended use.

All labels have the information required from the CMC perspective. The proposed proprietary name, TOBI Podhaler, was found acceptable by DMEPA. The Instructions

Reference ID: 3187826

for Use (IFU) are under review by DMEPA and by the CDRH ODE / DAGID / ARDB Human Factors Pre-Market Evaluation Team. The potential issues with the drug product / device may or may not be addressable by improvements to the Instructions for Use (IFU).

The package insert includes information regarding emitted dose delivered from the mouthpiece under specified in vitro conditions, as is recommended in the Draft Guidance - Guidance for Industry Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products, Chemistry, Manufacturing, and Controls Documentation, 1998.

GMP inspections of several facilities, including the drug product manufacturing site are incomplete. The Office of Compliance has therefore not issued an overall recommendation at this time.

Therefore this NDA is not recommended for approval until an overall acceptable recommendation is made by the Office of Compliance.

III. Administrative

A. Reviewer's Signature

{see electronic signature page}
Mark R. Seggel, Chemist

B. Endorsement Block

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

C. CC Block

{see darrts}

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

Reference ID: 3187826

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 SEGGEL
09/12/2012

RAPTI D MADURAWE
09/12/2012

Initial Quality Assessment
Branch V
Division of New Drug Quality Assessment II

OND Division:	Division of Anti-Infective Products (DAIP)
NDA:	201-688
Applicant:	Novartis Pharmaceutical Corporation
Stamp Date:	December 21, 2011
Proposed Trademark:	TOBI® Podhaler™ (*proposed name*)
Established Name:	Tobramycin inhalation powder
Dosage Form:	Inhalation powder
Route of Administration:	Oral inhalation
Strength:	28 mg
Indication:	Management of cystic fibrosis patients with *Pseudomonas aeruginosa*
Reviewer:	Mark Seggel, Ph.D.

	YES	NO
Acceptable for filing:	☒	☐
Comments for 74-Day Letter	☐	☒

Background

The drug product proposed via this NDA 505(b)(1), TOBI® Podhaler™ (tobramycin inhalation powder), is indicated for the management of cystic fibrosis patients with *Pseudomonas aeruginosa* (which is the same indication as for TOBI® (tobramycin inhalation solution) approved via NDA 50-753).

TOBI® Podhaler™ is a new formulation of tobramycin for inhalation to be delivered with a dry powder inhaler (T-326 Inhaler). TOBI® Podhaler™ was developed as a treatment alternative to TOBI® and designed to deliver high concentrations of tobramycin directly to the site of infection in the endobronchial space. The applicant claims that TOBI® Podhaler™ provides a more convenient treatment alternative for the heavily treatment burdened cystic fibrosis patients.

The stamp date for this NDA is December 21, 2011. As established by DAIP, this NDA will be reviewed on a standard (10 month) timeline with the PDUFA goal date of October 19, 2012.

NDA contains QbD elements and a design space is described for a drug product manufacturing unit operation. There are no reduced testing or RTRT schemes in the NDA.

IND Development

Reference ID: 3092355

The proposed drug product has been developed under IND 64,409. Per agreement at the pre-NDA meeting on December 15, 2009, reference is also made to selected information previously submitted to NDA 50-753 [TOBI® (tobramycin inhalation solution)].

The discussion and agreements reached during several meetings held throughout the drug development are available from DARRTS. Pertinent meetings include:

1) EOP2 Meeting - October 6, 2004

2) CMC EOP2 Meeting - July 18, 2005

3) Type A Meeting - November 8, 2007

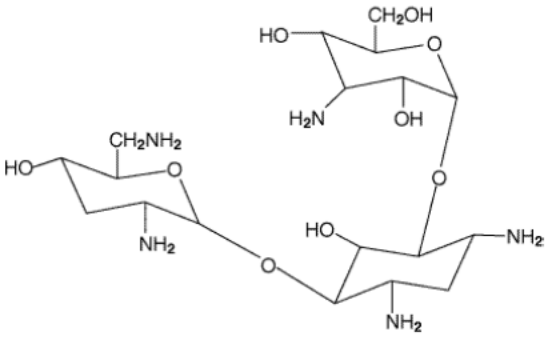
4) pre-NDA Meeting - December 15, 2009

5) Type A Phase 3 Clinical Development Meeting - February 1, 2011 (which included discussion of usability study, termination of study C2303, and labeling issues)

Review Notes

Drug Substance

Tobramycin belongs to the aminoglycoside class of antibiotics. The compound is a member of a broad-spectrum antibiotic complex, nebramycin, isolated from the fungus *Streptomyces tenebrarius*. It is a white or almost white powder, and is freely water-soluble.



Per agreements at the December 15, 2009 pre-NDA meeting, all CMC drug substance information is referenced to NDA 50-753 and two DMFs Type II [redacted] (b) (4) and [redacted] (b) (4) (also referenced in NDA 50-753). However, per agreements during the pre-NDA meeting, some general information (i.e. section 3.2.S.1) and the current specification for the tobramycin drug substance are provided in the current NDA. In addition, a list of post approval drug substance changes submitted to NDA 50-753 is included in the current NDA (Module 2).

Tobramycin drug substance is manufactured by two manufacturers, [redacted] (b) (4). (DMF Type II [redacted] (b) (4)) and [redacted] (b) (4)), which holds and DMF [redacted] (b) (4). *Comment: A list of*

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all DMFs and their status is provided in Appendix I, below; annual updates and/or amendments will need to be reviewed.

The following specification for the tobramycin drug substance has been proposed in the NDA:

The requirements listed below are valid at release and throughout shelf-life unless indicated otherwise.

Test Code	Title of Test, Principle	Requirements	Test performed for	
			Batch Release	Re-test
Description				
10001.02 (Ph. Eur)	Appearance by visual examination	White or almost white powder; visually free from any foreign contamination	+	+
Properties				
10046.02 (TM 007)	Color	Not more than (b) (4)	+	+
10201.02 (Ph. Eur., USP)	pH	(b) (4)	+	-
Identity				
20101.02 (USP)	Identification A by TLC	Corresponds to the reference	+	-
53001.02 (USP, TM 002)	Identification B by HPLC	Corresponds to the reference	+	-
Ph. Eur.	Identification B by TLC	Corresponds to the reference	F_1	-
Ph. Eur.	Identification C – color reaction	(b) (4)	+	-
Impurities				

(b) (4)

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Test Code	Title of Test, Principle	Requirements	Test performed for	
			Batch Release	Re-test
Impurities (cont'd)				
[redacted] (b) (4)				
70151.01 (Ph.Eur, USP, JP)	Microbial Enumeration Tests (MET):			
	• Total aerobic microbial count (TAMC)	[redacted] (b) (4)	+	-
	• Total combined yeasts/ moulds count (TYMC)		+	-
	• Specified micro-organisms (Pseudomonas aeruginosa, Staphylococcus aureus, Bile-tolerant gram-negative Bacteria)		+	-
70311.02 (Ph. Eur., USP)	Bacterial Endotoxins Test (BET)	[redacted] (b) (4)	+	-

Assay				
53001.02 (USP, TM 002)	Assay by HPLC: [redacted] (b) (4)	[redacted] (b) (4)	+	+
Ph. Eur.	Assay by HPLC	[redacted] (b) (4)	F_1	-

+ = mandatory

- = not required

F_1 = From supplier C o A

F_2 = [redacted] (b) (4)

F_3 = [redacted]

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Comment: *As recommended by the Agency at the EOP2 meeting, the endotoxins test has been included in the drug substance specification for this NDA. The proposed endotoxins and microbial limits tests and acceptance criteria should be consulted with the OPS Microbiology Product Quality Staff. It would be beneficial to compare the drug substance specification proposed in the current NDA with the tobramycin specification approved via referenced NDA 50-753, specifically, via recent CBE-0 supplement to this NDA, S-013 (approved on September 19, 2011).*

Drug Product

The drug product (TBM100, 28 mg inhalation powder hard capsule) is a white to almost white powder filled into size #2 clear, hypromellose capsules imprinted in blue ink with the text "NVR AVCI" on one half and "⏻" on the other half of the capsule:

The recommended dosage of TOBI® Podhaler™ for both adults and pediatric patients 6 years of age and older is the inhalation of the contents of four TOBI® Podhaler™ capsules, 28 mg each (corresponds to a target delivered dose of 25.5 mg tobramycin per capsule) twice-daily for 28 days using the Podhaler inhaler. Dosage is not adjusted by weight. All patients should be administered four 28 mg capsules twice daily.

Each TOBI® Podhaler package is a 4-week (28-day) supply containing four individual weekly packs (each pack is a 1-week supply), one reserve Podhaler inhaler (to be used if needed) and its storage case.

Each weekly pack of TOBI Podhaler contains one Podhaler inhaler and its storage case and seven blister cards (one card for each day of the week).

Each blister card contains eight (8) TOBI Podhaler capsules (four capsules for inhalation in the morning and four capsules for inhalation in the evening).

TBM100 inhalation powder is manufactured by spray-drying an oil-in-water emulsion (using Novartis' proprietary PulmoSphere™ formulation technology). The manufacturing process for TBM100 28 mg inhalation powder hard capsules utilizes the following operations: [redacted] (b) (4).

The components and composition of the powder, capsule shell and printing ink are outlined below:

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Table 2-1 Composition of one TBM100 28 mg Inhalation powder hard capsule

Ingredient	Theoretical amount per capsule (mg) [2]	Function	Reference to standards
Capsule fill			
Tobramycin	28.0	Active pharmaceutical ingredient	USP, Ph.Eur., Novartis monograph [3.2.S.4.1]
Sulfuric acid	(b) (4)	Salt forming agent and pH adjuster	NF, Ph.Eur.
1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC)		Wall forming agent	Novartis monograph [3.2.P.4.1]
Calcium chloride		Wall forming agent	Added as calcium chloride dihydrate, USP, Ph.Eur., JP
Water for Injection [1]		Processing aid	USP, Ph.Eur.
Perflubron [1]		Processing aid and pore forming agent	USP
Capsule fill weight			
(b) (4)		(b) (4)	See Table 2-2, Novartis monograph [3.2.P.4.1]
Total capsule weight	**105.6** [2]		

[1] Processing aid removed to residual levels

(b) (4)

Table 2-2 Capsule shell composition

Capsule shell component	Percentage per capsule	Function	Reference to standards
Hypromellose	(b) (4)	(b) (4)	USP, Ph.Eur.
(b) (4)			USP, Ph.Eur.
			NF, 2009/10/EC
			USP, Ph.Eur.
			See Table 2-3
			NF, Ph.Eur.

Table 2-3 Qualitative composition of Printing Ink - Blue

Printing ink component	Reference to standards
(b) (4)	USP/NF, Ph.Eur.
	21CFR, 2008/128/EC
	NF
	21CFR, 2008/128/EC
	USP, Ph.Eur.
	USP, Ph.Eur.

Sulfuric acid, calcium chloride dihydrate, water for injection and perflubron used in the TBM100 inhalation powder formulation are pharmaceutical grade complying with the quality requirements of the applicable USP/NF and Ph. Eur. monographs.

DSPC (distearoylphosphatidylcholine; 1,2-distearoyl-sn-glycero-3-phosphocholine) is not a compendial excipient. DSPC was chosen based on its (b) (4) properties as a wall-forming agent in the spray-dried formulation. It is stated that no excipients of human or animal origin are used during the manufacture of the drug product. *Comments: The applicant has mentioned other inhaled and intratracheal drug products containing DSPC and calcium*

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chloride. Also, the applicant has referred to the tox studies, which were conducted to establish safety of the above mentioned components for the inhalation route. These statements including the proposed levels of DSPC and calcium chloride in the current product should be verified with the pharm/tox reviewer. The proposed specifications including the endotoxins testing should be evaluated. Two suppliers of DSPC are listed in the NDA and reference to their respective DMFs Type IV provided (see Appendix I). Amendments to these two DMFs referenced for DSPC and one for HPMC would need a review. The quality (including purity) and important attributes of the drug product should be evaluated and compared for the two suppliers (drug product batches with DSPC from two sources were manufactured and placed on stability). (b) (4)

The applicant stated that over the course of development the manufacturing process was improved and validated for commercialization while maintaining the same composition, batch size, and general manufacturing sequence and steps.

Table 2-2 Unit formulas of the two formulation compositions studied during clinical development

Component	Formulation	
	TS-001[1]	CN1-002[2] (b) (4)

Powder for Phase III clinical supplies for studies C2301 and C2302 (subsequently referred to as Phase III process batches) was manufactured on the same spray dryer as Phase I supplies at a 3 kg batch size. Subsequently, changes were made to the Phase III process to improve stability of the emulsion and to reduce variability in powder yield without changing batch size and composition and delivery device. Per applicant, this modified process is referred to as the Improved (Pre-validation) process and was used to manufacture registration stability batches and to supply batches for the clinical study C2303:

Table 2-3 Powder manufacturing process development summary

Clinical study	Formulation	Manufacturing process nomenclature	Batch size	Key changes compared to Phase III
C2301	CN1-002	Phase III	3 kg	n/a
C2302	CN1-002	Phase III	3 kg	n/a
C2303	CN1-002	Improved (pre-validation)	3 kg	1. Emulsion stabilized with smaller droplet size 2. Powder hold-up and variability reduced with changes in collection hardware, (b) (4)
C2303	CN1-002	Improved (validated)	3 kg	Transfer to commercial equipment of like-design

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The Pharmaceutical Development section (about 90 pages) describes performing a DoE in the [redacted] (b) (4) Also, a set of DoE was performed to define the knowledge space, design space and to identify the control space (within the design space) for the spray-drying process. Several process parameters have been discussed and identified as critical. *Comment: The QbD Liaison (Dr. Lin Qi) will be consulted in evaluating the QbD aspects of the manufacturing process. Also, the Product Quality and Manufacturing Memo (PQM Memo) should be prepared for the drug product manufacturing facility in consultation with the QbD Liaison.*

In vitro aerosol and physicochemical characterization data to demonstrate comparability of the Phase III and Improved processes have been provided in section 3.2.P.2.3.5. These studies include: aerodynamic particle size distribution (APSD) including APSD profiles and mass per stage comparison; delivered dose uniformity and physical characterization (primary particle size, scanning electron microscopy, surface area and porosity, water content, DSC, XRPD, Raman). In addition, as described above, per agreement at the EOP2 meeting, a clinical study (C2303) was performed (and results provided in the NDA) using tobramycin inhalation powder manufactured by the modified process (TIP_{new}). *Comment: Comparability of C2303 batch to the C2301 and C2302 batches appears to be one of the most critical review issues for this NDA. A consultation with the biopharmaceutics group may be valuable to evaluate data from these studies. Also, early discussions with the clinical pharmacology reviewer should be initiated to evaluate overall bridging data for the product manufactured before and after process improvements.*

Drug product specification proposed in the NDA (reproduced in Appendix II, below) includes the following attributes: appearance (contents and shell), ID (by HPLC and IR), aerodynamic particle size distribution by NGI, uniformity of delivered dose by HPLC, degradation products, degradation product S-lyso-PC, water content, light obscuration particle count test, assay, uniformity of dosage units by content uniformity (HPLC), and microbial limits.

Tests that are not proposed in the specification include: polymorphism, residual perflubron, microscopic examination, DPSC content, bacterial endotoxin test and quantitative test for color of the capsule content. *Comments: The test microbial limits test and justification for not including endotoxin test should be consulted with the OPS Product Quality Microbiology Team. Does the drug product comply with ICHQ3C and USP <467> taking into consideration residual solvents that may be present in the drug substances and the excipients? Other issues regarding specification that may require a closer look include* [redacted] (b) (4) *, the target delivered dose (102 mg) versus final commercial dose (112 mg tobramycin = four 28 mg capsule) - is it justified?; also, the proposed limit for degradation product S-lyso-PC and other deg products including qualification issue, which may be consulted with the pharm/tox reviewer. If necessary, it may be valuable to discuss the proposed attributes, which are specific for the inhalation powders with the CMC reviewers in Branch VIII that supports the Pulmonary Division.*

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As mentioned above, the finished capsules are packaged in laminated aluminum-aluminum "peel-foil" unit dose blisters. Section 4 of 3.2.P.2 includes some information on the toxicological evaluation of the blisters (i.e., extractables and leachables). *Comment: Although some information on type and levels of extractables is provided in Tables 4-1 and 4-2, details of these studies have not been found. Additional information may be provided in DMF* (b) (4) *These results may be discussed with the pharm/tox reviewer as necessary*.

TBM100 inhalation powder is delivered by the T-326 Inhaler, which is a hand-held, manually-operated, breath-activated, unit-dose dry-powder inhaler that uses no batteries or electronics. Flow produced by patient inhalation evacuates the inhalation powder from the capsule, disperses particles into the inspiratory air stream, and delivers the drug into the lung. Characterization studies of the product have been performed and a summary is provided in Table 4-3 of the 3.2.P.2 section - Pharmaceutical Development (attached below as Appendix III). They include: stability of primary unprotected package; capsule/inhaler batch matching; effect of varying flow rates; dose build-up and flow resistance over an in-use period of 7 days; priming; effect of orientation; shaking and dropping (after capsule piercing); effect of patient use (e.g., planned return inhaler evaluation and clinical complaint inhaler evaluation; impact of vibration; shock and drop of the inhalation device; effect of moisture; photostability; device ruggedness; cleaning; and the primary stability studies described in 3.2.P.8. *Comments: Discussions with the medical team and pulmonary chemists will be valuable in evaluation of the results of these studies. Also, review of DMF* (b) (4) *may provide additional information, e.g., is there any information on leachables from the device? Consultation with CDRH is not requested at this time but will be initiated, if necessary, to evaluate specific aspects of the device design, construction and performance. These studies should be also reviewed in the context of their possible implications on the labeling, e.g., cleaning instructions.*

Registration stability studies have been conducted with three production-scale batches manufactured at Novartis Pharmaceuticals, San Carlos, USA: 36 months stability data are available on these production scale batches packaged in aluminum blister card (with and without overwrap). A 36 months shelf-life for TBM100 28 mg inhalation powder hard capsule along with the following storage conditions statement: "Store at 25 °C (77 °F). Excursions permitted to 15-30 °C (59-86 °F) [See USP Controlled room Temperature]. Protect from moisture." have has been proposed. *Comment: The packaging intended for the commercial use does not propose using an overwrap for the blisters.*

Labeling

Draft container and carton labels are provided in Module 1. The package insert is provided in the PLR format.

EES Information

All facilities involved in the manufacture of the proposed drug substance and the drug product were entered into EES by Althea Cuff on January 12, 2012. *Comments: A question was raised if the facility that manufactures the device should also be inspected. It should be noted that those facilities are not normally included in EERs for NDAs in the*

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Pulmonary Division and, therefore, it was not submitted to EES for the current NDA. The Product Quality and Manufacturing Memo (PQM Memo) for the drug product manufacturing facility should be prepared in consultation with the QbD Liaison.

Comparability Protocols

Several comparability protocols (CPs) have been proposed in this NDA (Section 3.2.R):

1. Comparability protocol for post-approval change in (b) (4) for T-326 Inhaler.
2. Comparability protocol for post-approval addition of an alternate supplier of DSPC.
3. Comparability protocol for post-approval addition of supplier capsule shell.
4. Comparability protocol for post-approval addition of an alternate primary packaging site.
5. Comparability protocol for post-approval change in batch size (b) (4)
6. Comparability protocol for post-approval change in (b) (4) manufacturing.

Each CP contains the following sections:

1. Objective
2. Description of planned changes
3. Specific tests and studies to be performed
4. Acceptance Criteria
5. Documentation to be provided in the submission under comparability protocol
6. Reporting category
7. Equivalence not demonstrated under this protocol
8. Commitment

Comment: These CPs will be reviewed by Dr. Brian Rogers from Branch VI.

Comments/Recommendations

Based on the information submitted, this NDA was judged to be complete for filing from the CMC perspective. There are no comments for inclusion in the 74-day letter. Issues, which may merit more discussion, are highlighted above as *Comments* in this IQA. A consultation from the OPS Microbiology Product Quality and ONDQA Biopharmaceutics groups should be requested. PQM Memo should be prepared for the drug product manufacturing facility.

Dorota Matecka *See DARRTS*
CMC Lead Date

Rapti Madurawe *See DARRTS*
Branch Chief Date

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Appendix I

DMF Table

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	II	(b) (4)	Tobramycin	14-Apr-2009	Adequate on 06-Jun-2011 for NDA 201-820; subsequently one annual update
	II		Tobramycin	10-Apr-2009	Adequate (b) (4)
	IV		DSPC	09-May-2011	Last review dated 10-Nov-2003; subsequently several annual updates and amendments
	IV		DSPC	05-Aug-2011	Last review dated 12-Oct-2003; subsequently several annual updates and amendments
	IV		Hard hypromellose capsule	27-Feb-2009	Last review dated 20-Oct-2005; subsequently two amendments
	III		(b) (4)	01-Dec-2010	Last review dated 14-May-2010 (item reviewed to be verified); subsequently two amendments and update
	III		T-326 Inhaler Inhaler case	11-Mar-2009	No review; IR sent on 18-Feb-2010

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Appendix II

Drug Product Specification

Test Code	Title of Test, Principle	Requirements	Test performed for	
			Batch release	Stability studies
Description				
10071.01	Appearance of contents	White to almost white powder, no visible foreign particulate matter.	+	+
10081.01	Appearance of shell			
	▪ Aspect	Clear colorless cap and body	+	+
	▪ Imprint	"NVR AVCI" in blue radial imprint on the capsule cap and "℄" in blue radial imprint on the capsule body" or "NVR AVCI" in blue radial imprint on the capsule body and "℄" in blue radial imprint on the capsule cap".	+	–
	▪ Size	Capsule size 2	+	–
10353.01	Aerodynamic particle size distribution by Next Generation Impactor (NGI) Stage groupings • Group 2 (Stages 1 + 2) • Group 3 (Stages 3 + 4) • Group 4 (Stages 5 to filter)	(b) (4)	+	+
Identification				
20551.01	Identification by FTIR (ATR)			
	▪ Tobramycin	Corresponds to the reference spectrum	+	–
59001.01	Identification by HPLC			
	▪ Tobramycin	Corresponds to the reference	+	–

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Test Code	Title of Test, Principle	Requirements	Test performed for	
			Batch release	Stability studies
Performance				
50211.01	Uniformity of delivered dose by HPLC			
	▪ Tobramycin, single delivered dose, four-capsule set		+	+
	Outside ± 20 % of mean delivered dose	(b) (4)		
	Outside ± 25 % of mean delivered dose			
	▪ Tobramycin, mean delivered dose, four-capsule set		+	+
Impurities				
31001.01	Degradation products by HPLC, based on the declared content of Tobramycin			
	Specified identified			
	▪ (b) (4)	(b) (4)	+	–
			–	+
	▪ (b) (4)		+	–
			–	+
	Specified, unidentified			
	(b) (4)		+	–
			–	+
	Any unspecified		+	+
	Total unspecified		+	+
	Total degradation products		+	–
			–	+
31011.01	Degradation product by HPLC			
	▪ S-lyso-PC (1-stearoyl-2-lyso-sn-glycero-3-phosphocholine), based on the declared powder content per capsule	(b) (4)	+	+

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Test Code	Title of Test, Principle	Requirements	Test performed for	
			Batch release	Stability studies
35812.01	Water by Karl Fischer (coulometric with oven)	(b) (4)	+	+
35813.01	Water by Karl Fischer (coulometric with oven and autosampler) (Alternate method to 35812.01)		+	+
70161.01	Microbial enumeration tests (Plate-count method)			
	▪ Total aerobic microbial count (TAMC)	(b) (4)	+	(+)
	▪ Total combined yeasts/ molds count (TYMC)		+	(+)
	▪ Specified micro-organisms		+	(+)
			+	(+)
			+	(+)
37321.01	Light obscuration particle count test	(b) (4)	+	-
Assay				
59001.01	Assay by HPLC			
	▪ Tobramycin	(b) (4)	+	+
59001.01	Uniformity of dosage units by content uniformity by HPLC			
	▪ Tobramycin	Meets the requirements of Ph. Eur., USP and JP (harmonized procedure)	+	–

+ = Parameter routinely tested

– = Parameter NOT tested

(+) = optional (as defined in appropriate stability protocol)

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Appendix III

Table 4-3 Drug product characterization summary and labeling impact

Study	Section	Conclusions	Impact on Labeling
Determination of appropriate storage conditions	Section 4.3.1	Drug product is stable under the proposed storage conditions. The primary packaging adequately protects the drug product from moisture.	Expiry dating
Stability of primary (unprotected) package	Section 4.3.2	In-use stability data support the proposed drug product instructions for use.	Patients instructed to dose immediately after removing capsules from blister
Capsule/inhaler batch matching	Section 4.3.3	Comparable aerosol performance regardless of inhaler batch and capsule batch used	No specific statements in the labeling
Effect of varying flow rates	Section 4.3.4	Comparable aerosol performance was obtained throughout an airflow range of (b) (4) LPM, which is most relevant to cystic fibrosis patients.	No specific statements in the labeling
Effect of storage of the drug product on the particle size distribution	Section 4.3.5	No impact on aerosol performance	Expiry dating
Dose build-up and flow resistance	Section 4.3.6	No impact on aerosol performance through-inhaler life	T-326 Inhaler use life 7 days
Priming	Section 4.3.7	No priming effect	No specific statements in the labeling
Effect of orientation	Section 4.3.8	Orientation of the inhaler during dosing does not affect aerosol performance. Dropping and shaking the inhaler after capsule piercing has no impact to aerosol performance.	No specific statements in the labeling however patient is instructed to not use a dropped or damaged inhaler
Effect of patient use	Section 4.3.9	Drug product performance after use is acceptable and limited product performance complaints received	No specific statement in the labeling however patient is instructed to not use a dropped or damaged device, and to store inhaler in case and keep away from moisture.
Effect of moisture	Section 4.3.10	Aerosol performance is affected at high humidity conditions	Store inhaler in case, keep away from moisture. Use capsule as soon as removed from the blister card.
Photostability	Section 4.3.11	TBM100 28 mg Inhalation powder hard capsule shows no sensitivity to light	No specific statements in the labeling
Device Ruggedness	Section 4.3.12	The T-326 Inhaler is able to withstand the forces applied during controlled engineering studies and home-based clinical trials	No specific statements in labeling; however patient is instructed to not use a dropped or damaged inhaler
Cleaning Instructions	Section 4.3.13	Cleaning procedure adequate	Use a clean dry cloth to wipe exterior mouthpiece

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/s/

DOROTA M MATECKA
02/24/2012

RAPTI D MADURAWE
02/27/2012