

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

201688s000

OTHER REVIEW(S)

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information	
NDA # 201,688 BLA# N/A	NDA Supplement #:S- N/A BLA STN # N/A
Efficacy Supplement Type SE- N/A	
Proprietary Name: TOBI Podhaler Established/Proper Name: Tobramycin inhalation powder Dosage Form: Inhalation powder hard capsule Strengths: 28 mg	
Applicant: Novartis Pharmaceuticals Corporation Agent for Applicant (if applicable): N/A	
Date of Application: December 21, 2011 Date of Receipt: December 21, 2011 Date clock started after UN: N/A	
PDUFA Goal Date: October 19, 2012	Action Goal Date (if different): N/A
Filing Date: February 17, 2012	Date of Filing Meeting: January 31, 2012
Chemical Classification: (1,2,3 etc.) (original NDAs only) Aminoglycosides – Systemic (4010500)	
Proposed indication(s)/Proposed change(s): Management of Cystic Fibrosis patients with <i>Pseudomonas aeruginosa</i> .	
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	X 505(b)(1) N/A
<i>If 505(b)(2): Draft the “505(b)(2) Assessment” form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>	
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	X Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? No	Resubmission after refuse to file? No
Part 3 Combination Product? Yes <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input checked="" type="checkbox"/> Other (drug/device/biological product)

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product): N/A				
List referenced IND Number(s): IND 64,409				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
<i>If yes, explain in comment column.</i>			X	
<i>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:</i>			X	
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input type="checkbox"/> Paid <input checked="" type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>			<p>X</p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>			<p>X</p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i></p>			<p>X</p>																	
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the <i>Electronic Orange Book</i> at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1446 1349 1587"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration															<p>X</p>	
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? Check the <i>Orphan Drug Designations and Approvals</i> list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</p>	<p>X</p>																			

If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>	X			
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>) If yes, # years requested: <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>		X		
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?		X		
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>			X	

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

1

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

<input type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input type="checkbox"/> pagination <input type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?			X	
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?			X	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature?	X			

<p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>				
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			X	

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>		X		Drug has Orphan status
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>			X	

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

If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>			X	
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>			X	
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>		X		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	X			
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the DCRMSRMP mailbox</i>		X		
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	X			
Is the PI submitted in PLR format? ⁴	X			

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

⁴ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	X Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	X			
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	X			
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>	X			
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	X			
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	X			
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s) Date(s): N/A <i>If yes, distribute minutes before filing meeting</i>				

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): December 15, 2009 <i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s): June 7, 2007 (CMC) <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: January 31, 2012

NDA #: 201,688

PROPRIETARY NAME: TOBI Podhaler

ESTABLISHED/PROPER NAME: Tobramycin Inhalation Powder

DOSAGE FORM/STRENGTH: 28mg

APPLICANT: Novartis Pharmaceuticals Corporation

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Management of Cystic Fibrosis patients with *Pseudomonas aeruginosa*.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	J. Christopher Davi, MS	Y
	CPMS/TL:	Maureen Dillon-Parker	Y
Cross-Discipline Team Leader (CDTL)	TBD		
Clinical	Reviewer:	Shrimant Mishra, MD	Y
	TL:	Eileen Navarro-Almario, MD	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:	N/A	
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:	N/A	
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	Peter Coderre, PhD, MBA	Y
	TL:	Fred Marsik, PhD	Y

Clinical Pharmacology	Reviewer:	Ryan Owen, PharmD	Y
	TL:	Kimberly Bergman, PharmD	Y
Biostatistics	Reviewer:	Christopher Kadoorie, PhD	Y
	TL:	Thamban Valappil, PhD	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Amy Ellis, PhD	Y
	TL:	Wendelyn Schmidt, PhD	Y
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:	N/A	
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:	N/A	
	TL:	N/A	
Product Quality (CMC)	Reviewer:	Mark Seggel, PhD	Y
	TL:	Dorota Mateka, PhD	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	N/A	
	TL:	N/A	
CMC Labeling Review	Reviewer:	N/A	
	TL:	N/A	
Facility Review/Inspection	Reviewer:	Mark Seggel, PhD	Y
	TL:	Dorota Mateka, PhD	Y
OSE/DMEPA (proprietary name)	Reviewer:	TBD	
	TL:	TBD	
OSE/DRISK (REMS)	Reviewer:	TBD	
	TL:	TBD	
OC/OSI/DSC/PMSB (REMS)	Reviewer:	N/A	
	TL:	N/A	

Bioresearch Monitoring (DSI)	Reviewer:	N/A	
	TL:	N/A	
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:	N/A	
Other reviewers			
Other attendees			

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments: None</p>	<input type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments: None</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Advisory Committee Meeting needed? <p>Comments: None</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety</i> 	<input checked="" type="checkbox"/> YES Date if known: September 5, 2012 <input type="checkbox"/> NO <input type="checkbox"/> To be determined Reason: TBD

<p><i>or efficacy issues</i></p> <ul style="list-style-type: none"> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	
<ul style="list-style-type: none"> • Abuse Liability/Potential <p>Comments:</p>	<p>X Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<ul style="list-style-type: none"> • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<p>X Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable X FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable X FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<ul style="list-style-type: none"> • Clinical pharmacology study site(s) inspections(s) needed? 	<p><input type="checkbox"/> YES X NO</p>
<p>BIOSTATISTICS</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable X FILE <input type="checkbox"/> REFUSE TO FILE</p> <p>X Review issues for 74-day letter</p>
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable X FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>

<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p style="padding-left: 40px;">If no, was a complete EA submitted?</p> <p style="padding-left: 40px;">If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>

<u>CMC Labeling Review</u>	
Comments: None	<input type="checkbox"/> Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: John Farley, MD (Division Sign-off)	
21st Century Review Milestones (see attached) (listing review milestones in this document is optional):	
Comments: None	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why: N/A
X	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. X Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> X Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)

	<ul style="list-style-type: none"> • notify DMPQ (so facility inspections can be scheduled earlier)
<input type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
<input type="checkbox"/>	Other

J. Christopher Davi
Regulatory Project Manager

August 14, 2012
Date

Appendix A (NDA and NDA Supplements only)

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

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

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

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

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

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

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

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

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

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

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

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

/s/

JOSEPH C DAVI
03/27/2013

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA/BLA # 201688
Product Name: TOBI Podhaler

PMR/PMC Description: **1928-1** A prospective, observational study in the United States, which includes a five year period of time after introduction of the TOBI Podhaler to the market to determine if decreased susceptibility to tobramycin is increasing in *Pseudomonas aeruginosa* from cystic fibrosis (CF) patients. The study will enroll 500 patients. This study should also monitor resistance to these additional antibacterial drugs: meropenem, imipenem, ceftazidime, aztreonam and ciprofloxacin. Within the study, the following treatment emergent pathogens should be evaluated: *Staphylococcus aureus*, *Stenotrophomonas maltophilia*, *Achromobacter xylosoxidans*, and *Burkholderia* spp. Provide a detailed protocol to the Agency for review and comment prior to commencing the study. Interim reports of changes in *P. aeruginosa* susceptibility and treatment-emergent pathogens from CF patients should be submitted annually for the duration of the study period. After the first year, the report should be cumulative. The Agency may consider this postmarketing requirement fulfilled after three years if the data do not warrant a longer surveillance period.

PMR/PMC Schedule Milestones:	Final protocol submission:	12/2013
	First interim report:	5/2016
	Second interim report:	5/2017
	Third interim report:	5/2018
	Fourth interim report:	5/2019
	Fifth interim report:	5/2020
	Study completion date:	2/2021
	Final report submission:	7/2021

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The microbiology review of the NDA noted a signal of potentially increased resistance of *Pseudomonas aeruginosa* to tobramycin with TOBI Podhaler relative to the nebulized tobramycin formulation already on the market. It is unclear what the mechanism or clinical consequence of this is. Further microbiologic surveillance is indicated.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The primary intent of this study is to monitor whether *Pseudomonas aeruginosa* isolates from cystic fibrosis patients are exhibiting increased rates of resistance to tobramycin and other antimicrobials after the introduction of TOBI Podhaler in the market. Such findings were noted pre approval but it was unclear how prevalent of an issue this was and whether it had any impact clinically. The microbiologic surveillance data gathered from this study will help to answer these questions.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A prospective observational study in 500 U.S. cystic fibrosis patients to monitor resistance to these additional antibacterial drugs: meropenem, imipenem, ceftazidime, aztreonam and ciprofloxacin

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

Other

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs? Yes
- Are the objectives clear from the description of the PMR/PMC? Yes
- Has the applicant adequately justified the choice of schedule milestone dates? Yes
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process? Yes

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA/BLA # 201688
Product Name: TOBI Podhaler

PMR/PMC Description: **1928-2** A one year, prospective observational cohort study in the United States of CF patients chronically colonized with *P. aeruginosa* who use TOBI Podhaler as part of their regular care compared to patients using other FDA approved inhaled antipseudomonal antibacterial drugs to assess clinical outcomes, including patients with increased *P. aeruginosa* minimum inhibitory concentrations to tobramycin at baseline. The study will enroll 500 patients. The clinical outcomes should include use of other antipseudomonal antibacterial drugs, non-respiratory and respiratory-related hospitalizations, mortality, and changes in FEV₁% predicted from baseline. This study should also include sputum pharmacokinetics and assess changes in *P. aeruginosa* sputum log₁₀ CFU/g. Within the study, the following treatment emergent pathogens should be evaluated: *Staphylococcus aureus*, *Stenotrophomonas maltophilia*, *Achromobacter xylosoxidans*, and *Burkholderia spp.* This study should utilize appropriate approaches to the design and statistical analysis (e.g., baseline covariates, propensity scores) to account for potential differences between the treatment cohorts.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>12/2013</u>
	Study/Trial Completion:	<u>02/2017</u>
	Final Report Submission:	<u>07/2017</u>

6. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The clinical review of the NDA noted that despite improvements in pulmonary function with TOBI Podhaler compared to placebo, there was increased usage of other antipseudomonals with TOBI Podhaler as compared to the current nebulized tobramycin product currently on the market. Despite this concern, it was felt that enough benefit had been shown in terms of overall efficacy and potential for ease of use that the product should be approved while evaluating the above concern as a post-marketing requirement.

7. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The primary intent of this study is to monitor whether pertinent clinical outcomes, such as hospitalizations, antipseudomonal usage, mortality, and pulmonary function parameters differ between cystic fibrosis patients using TOBI Podhaler as part of their regular care and those using other approved alternatives.

8. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

9. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A prospective observational cohort study in 500 U.S. cystic fibrosis patients

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

Other

10. Is the PMR/PMC clear, feasible, and appropriate?

Does the study/clinical trial meet criteria for PMRs or PMCs? Yes

Are the objectives clear from the description of the PMR/PMC? Yes

Has the applicant adequately justified the choice of schedule milestone dates? Yes

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process? Yes

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # 201688
Product Name: TOBI Podhaler

PMR/PMC Description: **1928-3** An actual use human factors study to validate the approved Instructions for Use (IFU). The study will enroll 45 patients in total with three age groups of 15 patients each: 6-10 years, 11-17 years, and > 18 years. Only CF patients naïve to use of the Podhaler device will be enrolled. These patients will not be trained prior to reading the IFU and will be observed during the study.

PMR/PMC Schedule Milestones:	Draft Protocol Submission:	<u>08/2013</u>
	Final Protocol Submission:	<u>02/2014</u>
	Study/Trial Completion:	<u>05/2015</u>
	Final Report Submission:	<u>08/2015</u>

11. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The human factors analysis of the NDA noted that the pre approval human factors studies were insufficient, particularly with regards to validation of the Instructions For Use. Though it was felt that cystic fibrosis patients are quite experienced with the usage of various medical devices and have closely coordinated medical care, there were lingering concerns about whether the TOBI Podhaler might be used incorrectly, particularly in younger patients. Thus, this post-market study will assess any difficulties in understanding and following the Instructions For Use so that appropriate adjustments can be made if necessary.

12. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The primary intent of this study is to assess whether cystic fibrosis subjects of various age groups can understand and follow the Instructions For Use for TOBI Podhaler.

13. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

14. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

An actual use observational cohort study in 45 cystic fibrosis patients naïve to the use of TOBI Podhaler.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

-
- Other
-

15. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs? Yes
- Are the objectives clear from the description of the PMR/PMC? Yes
- Has the applicant adequately justified the choice of schedule milestone dates? Yes
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process? Yes

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # 201688
Product Name: TOBI Podhaler

PMR/PMC Description: **1928-4** Create adjunct instructions for use using alternative media and validate these instructions for use to ensure the patient can safely and effectively perform the critical tasks for the intended use of this product.

PMR/PMC Schedule Milestones:	Draft Protocol Submission:	<u>09/2013</u>
	Final Protocol Submission:	<u>05/2014</u>
	Study/Trial Completion:	<u>08/2015</u>
	Final Report Submission:	<u>11/2015</u>

16. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Given that cystic fibrosis affects children as well as young adults, it was felt that alternative media, such as digital media, should be developed for the Instructions For Use in order to adapt to the ways such patient populations seek out information.

17. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The primary intent of this study is to develop and validate alternative media for the Instructions For Use

18. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

19. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Likely an actual use observational study but the study design will be decided upon in the future

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

-
- Other
Study related to safe drug use
-

20. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs? Yes
- Are the objectives clear from the description of the PMR/PMC? Yes
- Has the applicant adequately justified the choice of schedule milestone dates? Yes
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process? Yes

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

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

/s/

JOSEPH C DAVI
03/22/2013

SUMATHI NAMBIAR
03/22/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Final Label and Labeling Review

Date: March 20, 2013

Reviewer: Aleksander Winiarski, PharmD
Division of Medication Error Prevention and Analysis

Team Leader: Jamie Wilkins Parker, PharmD
Division of Medication Error Prevention and Analysis

Drug Name and Strength: TOBI Podhaler (Tobramycin Inhalation Powder)
28 mg per capsule

Application Type/Number: NDA 201688

Applicant: Novartis Pharmaceuticals Corp.

OSE RCM #: 2012-2927

*** This document contains proprietary and confidential information that should not be released to the public.***

1 INTRODUCTION

This review evaluates the patient instructions for use, carton labeling, insert labeling, capsule blister label, and inhaler labels for TOBI Podhaler, NDA 201688, for revision to our previous comments to the Applicant in OSE review #2012-304, dated September 27, 2012.

2 REGULATORY HISTORY

TOBI (Tobramycin Inhalation Solution, USP), 300 mg/5 mL for use with nebulizers, was approved under NDA 050753 on December 22, 1997.

The Applicant seeks to expand the TOBI product line with the proposed drug product TOBI Podhaler (Tobramycin Inhalation Powder), 28 mg per capsule, under NDA 201688. The Agency issued a complete response to the Applicant on October 19, 2012, citing deficiencies related to facility inspections.

3 MATERIAL REVIEWED

DMEPA reviewed the revised patient instructions for use, carton labeling, insert labeling, capsule blister label, and inhaler labels submitted by the Applicant on November 27, 2012. See Appendices (A through E). We also evaluated our recommendations made in OSE review #2012-304 to assess whether the revisions adequately address our concerns from a medication error perspective.

4 CONCLUSIONS AND RECOMMENDATIONS

The revised patient instructions for use, carton labeling, insert labeling, capsule blister label, and inhaler labels adequately address our concerns from a medication error perspective. DMEPA concludes that the proposed labels and labeling are acceptable.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarification, please contact OSE Regulatory Project Manager, Karen Townsend, at 301-796-5413.

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

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

/s/

ALEKSANDER P WINIARSKI
03/20/2013

JAMIE C WILKINS PARKER
03/22/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Labels and Labeling Review

Date: September 27, 2012

Reviewer: Aleksander Winiarski, PharmD
Division of Medication Error Prevention and Analysis

Acting Team Leader: Jamie Wilkins Parker, PharmD
Division of Medication Error Prevention and Analysis

Division Deputy Director: Kellie Taylor, PharmD, MPH
Division of Medication Error Prevention and Analysis

Division Director: Carol Holquist, RPh
Division of Medication Error Prevention and Analysis

Drug Name and Strength: TOBI Podhaler (Tobramycin Inhalation Powder)
28 mg per capsule

Application Type/Number: NDA 201688

Applicant/sponsor: Novartis Pharmaceuticals Corp.

OSE RCM #: 2012-304

*** This document contains proprietary and confidential information that should not be released to the public.***

Contents

1	Introduction.....	1
1.1	Regulatory History and Background.....	1
1.2	Product Information	1
2	Methods and Materials Reviewed.....	1
2.1	Selection of Medication error Cases	2
2.2	Labels labeling and Usability Study	2
3	Medication Error Cases.....	3
4	Review of Label and Labeling.....	3
4.1	Blister pack label.....	3
4.2	Inhaler and inhaler cover label.....	4
4.3	Carton container labeling (containing 4 weekly packs).....	4
4.4	Weekly pack labeling (wallet) / Weekly Pack Labeling (wallet)– Sample.....	4
4.5	Insert Labeling	4
5	Conclusions.....	5
6	Recommendations.....	5
6.1	Comments to the Division.....	6
	Appendices.....	8

1 INTRODUCTION

This review evaluates the proposed patient instructions for use, carton labeling, insert labeling, capsule blister label, and inhaler labels for TOBI Podhaler, NDA 201688, for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY AND BACKGROUND

TOBI (Tobramycin Inhalation Solution, USP), 300 mg/5 mL for use with nebulizers, was approved under NDA 050753 on December 22, 1997.

The Applicant seeks to expand the TOBI product line with the proposed drug product TOBI Podhaler (Tobramycin Inhalation Powder), 28 mg per capsule, under NDA 201688, of which the label and labeling are the subjects of this review.

1.2 PRODUCT INFORMATION

The following product information is provided in the January 30, 2012 proprietary name submission:

- Active Ingredient: Tobramycin Inhalation Powder
- Indication of Use: Management of cystic fibrosis patients with *Pseudomonas aeruginosa*
- Route of Administration: Oral inhalation
- Dosage Form: Inhalation powder
- Strength: 28 mg per capsule
- Dose and Frequency: Inhalation of the contents of four 28 mg capsules twice daily for 28 days.
- How Supplied: Each individual weekly pack contains 1 Podhaler inhaler with storage case and 7 blister cards, containing 8 capsules per blister (1 blister for each day of the week). Each package contains 1 reserve Podhaler inhaler to be used if necessary, and a 4-week (28-day) product supply in 4 individual weekly packs.
- Storage: Room temperature
- Container and Closure Systems: Forming aluminum plastic foil, lidding foil is peelable with white lacquer and laminate, T-326 inhaler in sealed case.

2 METHODS AND MATERIALS REVIEWED

DMEPA searched the FDA AERS database for TOBI medication error reports. We also reviewed the TOBI Podhaler labels and package insert labeling submitted by the Applicant. However, because there are no other Tobramycin dry powder inhalers on the market and because the product characteristics between the TOBI inhalation solution and the TOBI Podhaler vary significantly, only wrong drug selection cases based on the root name “TOBI” and wrong frequency or duration of administration cases were considered

relevant to this review, as these are the overlapping product characteristics between the two products.

2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FDA Adverse Event Reporting System (AERS) using the strategy listed in Table 2.

Table 2: AERS Search Strategy	
Date Searched	March 21, 2012
Drug Names	TOBI
MedDRA Search Strategy	Medication Errors (HLGT) Product Quality Issues (HLGT)

The AERS database search identified 20 reports. Each report was reviewed for relevancy and duplication. After individual review, 18 reports were excluded for the following reasons: no medication error occurred, the medication errors were related to quality (e.g. discolored solution or solution that had a strong odor was administered), packaging or labels and labeling of other Tobramycin formulations [inhalation solution or ampoules (e.g. ampoules appear similar to other products, wrong technique in use of the TOBI solution)] that are different from the TOBI Podhaler.

2.2 LABELS LABELING AND USABILITY STUDY

Using the principles of human factors and Failure Mode and Effects Analysis,¹ along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Blister Pack Labels submitted 12/21/2011 (Appendix B)
- Inhaler and Inhaler Cover Label submitted 12/21/2011 (Appendix C)
- Carton Labeling (contains 4 Weekly Packs) submitted 12/21/2011 (Appendix D)
- Weekly Pack Carton Labeling (Wallet) submitted 12/21/2011 (Appendix E)
- Weekly Pack Carton Labeling (Wallet) - Sample submitted 12/21/2011 (Appendix F)
- Insert Labeling submitted 12/21/2011 (no image)

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

3 MEDICATION ERROR CASES

Following exclusions as described in section 2.1, two TOBI medication error cases remained and are summarized below.

Wrong duration of therapy and wrong frequency of administration (n=2)²

Two cases describe patients who were prescribed TOBI therapy inconsistent with the approved indication and/or approved dosage regimen. The first patient was an 88 year old male with bronchiectasis who was prescribed 300 mg of TOBI twice daily via nebulization. However, the reporting physician stated that the patient misunderstood the dispensing pharmacist regarding the dosing schedule and used the product continuously for 4 to 5 months instead of the intended 28 days on and 28 days off cycle, which resulted in an overdose leading to hospitalization due to acute renal failure.

The second patient was a 56 year old male who was prescribed TOBI 300 mg twice daily for an unspecified indication. The patient was confused about the prescribed dosage regimen and was taking the drug once daily, every day versus the intended twice daily schedule for 3 months on and 3 months off. The patient developed pancreatitis after starting the TOBI, however there were no other outcomes reported.

The TOBI Podhaler insert labeling states in the patient instructions for use subsection that the product should be inhaled every 12 hours and the package is a 28-day supply. However, there is no mention of the 28-day on and off cycles. This point could be clarified by adding information regarding the approved therapy regimen to the patient's instructions for use section of the labeling.

We also note, that based on medication errors with products that utilize capsules to deliver a powder for inhalation (e.g. Spiriva)³ it is reasonable to expect that some patients will swallow the TOBI Podhaler capsules, which may result in underdose. However, the product will not be redesigned to minimize this risk. Therefore, we need to ensure a statement is added to the labels and labeling that the product is for inhalation use only.

4 REVIEW OF LABEL AND LABELING

DMEPA identified the following deficiencies with the proposed TOBI Podhaler labels and labeling.

4.1 BLISTER PACK LABEL

- The two parts of the proprietary name TOBI podhaler appear in different fonts and incorporate a graphic (above TOBI). Additionally, the name is displayed inconsistently with the package insert labeling and with the name submission, where the 'P' in Podhaler was capitalized.
- The statement "DO NOT SWALLOW" appears in all capital letters which decreases readability and is more prominent than the statement "For inhalation

² ISR numbers: 4070503 and 8119504

³ OSE review #2011-1115 and 2011-2172

use only” which appears in smaller font using title letters. Since negative statements such as “Do Not” are often overlooked and title case is easier to read we will request this statement be modified.

- The statement “DO NOT push capsule through” is overly prominent in comparison to the statement “Peel back foil to reveal each capsule”.

4.2 INHALER AND INHALER COVER LABEL

- The inhaler cover is missing an expiration date.
- On the inhaler and the inhaler cover, the two parts of the proprietary name TOBI podhaler appear to be written in different fonts, different shades and incorporate a logo (above TOBI), which decrease the name’s readability. Additionally, the name is inconsistent with the package insert labeling and with the name submission, where the ‘P’ in Podhaler was capitalized.
- On the inhaler the statement “FOR USE ONLY WITH TOBI PODHALER CAPSULES” is written in all capital letters, which decreases readability.
- On the inhaler and the inhaler cover the “Rx Only” statement is missing.

4.3 CARTON CONTAINER LABELING (CONTAINING 4 WEEKLY PACKS)

- The two parts of the proprietary name TOBI podhaler appear to be written in different fonts, two colors and incorporate a logo (above TOBI), which decrease the name’s readability. Additionally, the name is inconsistent with the package insert labeling and with the name submission, where the ‘P’ in Podhaler was capitalized.
- The graphic (wavy lines) on the principal display panel and top panel is distracting and divides the panels. The names and strength are written on a smaller part of the panels and large parts of the panels are unused, which results in decreased prominence of the most important prescribing information.
- The statements “FOR ORAL INHALATION ONLY” and “CAPSULES SHOULD ALWAYS BE STORED IN THE BLISTER AND ONLY REMOVED IMMEDIATELY BEFORE USE” is written in all capital letters which decreases readability.

4.4 WEEKLY PACK LABELING (WALLET) / WEEKLY PACK LABELING (WALLET)–SAMPLE

- Same comments as above for Carton Labeling.

4.5 INSERT LABELING

- In the Dosage and Administration section, the sentence “... and resume therapy for the next 28 days on/28 days off cycle” uses the slash ‘/’ mark, which is on the Institute for Safe Medication Practices’ (ISMP) list of error-prone abbreviations.
- In the usability study subjects experienced some difficulty in deciding when they should or should not continue to inhale the capsules. In the instructions for use, step 12, the directions are unclear as to when to continue inhaling from the capsule (e.g. no mention of residue) and the corresponding picture may be

misleading in indicating how much powder is needed to require a patient to re-inhale. This issue has been addressed with the revised IFU.

- Based on the two TOBI post-marketing cases of wrong duration of therapy, the instructions for use may be improved by incorporating the approved duration and schedule of use into the directions.

Additionally, we identified wrong frequency/duration of use errors with the TOBI nebulizer ampoules. In these cases the patient took the product continuously instead of cycling on and off. Since TOBI and TOBI Podhaler have the same frequency of use and duration of therapy, to minimize these errors we recommended including this information in the Patient's Instructions For Use, under the 'How to inhale your medicine with the Podhaler inhaler' section. The IFU has been revised to adequately address this concern.

- In the Instructions For Use section, step 4, the two pictures are labeled as 'a' and 'b', this labeling is reused with subsequent steps and may cause confusion. We requested the graphics be relabeled as numeric steps 4, 5, and 10 so that so that the letters are not reused. Additionally, we requested descriptors be added (e.g. with lines or arrows) directly on the graphics to allow for clearer identification of the individual device/product components. The IFU has been revised to address these issues.

5 CONCLUSIONS

DMEPA concludes that the proposed label and labeling can be improved to increase the readability and prominence of important information on the label to promote safe use of the product.

6 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

A. Blister Pack Label

1. The two parts of the proprietary name TOBI podhaler appear to be written in different fonts and incorporate a graphic (above TOBI). Additionally, the name is presented inconsistently across your labeling. The name appears with a capital "P" in the package insert labeling. Therefore we request you revise the proprietary name to read "TOBI Podhaler". We request that the 'P' be capitalized, the root name TOBI unbolded, and the logo above TOBI removed.
2. The negative statement "DO NOT SWALLOW" appears in all capital case letters where as the statement "For inhalation use only" appears in a smaller font and in title case letters. Therefore, we request you revise the "Do not swallow" statement to appear in title case letters and in the same

font size as “For inhalation use only”. Furthermore, these statements should have equal prominence.

3. We request you revise the “DO NOT push capsule through” statement to appear in all title case letters. Additionally, we request you increase the prominence of the “Peel back foil to reveal each capsule” so that it is equally prominent with the statement “Do Not push capsule through...”.

B. Inhaler and Inhaler Cover Label

1. See A1 above. In addition, revise the proprietary name presentation to appear in a single font size and color.
2. Indicate where the expiration date will appear on the inhaler cover.
3. To improve readability, on the inhaler, revise the statement “FOR USE ONLY WITH TOBI PODHALER CAPSULES” to appear in title case letters.

C. Carton Labeling (Containing 4 weekly packs)

1. See A1 and B1 above.
2. The graphic (wave) on the principal display panel and top panel is too prominent. As such, this information becomes the focal point of the label rather than the most important information such as the product proprietary and established names and strength. Remove or minimize the graphic (wave) and increase the prominence of the proprietary name, established name and strength statements on the principal display panel.
3. To improve readability, revise the statements “FOR ORAL INHALATION ONLY” and “CAPSULES SHOULD ALWAYS BE STORED IN THE BLISTER AND ONLY REMOVED IMMEDIATELY BEFORE USE” to appear in title case letters.

D. Weekly Pack Carton Labeling (including Sample Pack)

1. See A1, B1, C2, and C3 above.

6.1 COMMENTS TO THE DIVISION

Insert Labeling

1. In the In the Full Prescribing Information Dosage and Administration section, the sentence “... and resume therapy for the next 28 days on/28 days off cycle.” uses the slash ‘/’ mark, which is on the Institute for Safe Medication Practices’ (ISMP)⁴ list of error-prone abbreviations and has been misinterpreted as the number “1”. Rephrase the sentence to “... and resume therapy for the next 28 days on and 28 days off cycle.”

⁴ Institute for Safe Medication Practices (ISMP). ISMP’s List of Error-Prone Abbreviations, Symbols, and Dose Designations. ISMP: 2010

2. In the Full Prescribing Information Dosage and Administration section, to clarify administration of the product, add a statement similar to: “Refer to the Patient Instructions For Use (PIFU) for full administration information”.

If you have further questions or need clarifications, please contact Karen Townsend, project manager, at 301-796-0150.

APPENDICES

Appendix A. Database Descriptions

Adverse Event Reporting System (AERS)

The Adverse Event Reporting System (AERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The FDA uses AERS to monitor adverse events and medication errors that might occur with these marketed products. The structure of AERS complies with the international safety reporting guidance ([ICH E2B](#)) issued by the International Conference on Harmonisation. Adverse events in AERS are coded to terms in the Medical Dictionary for Regulatory Activities terminology (MedDRA).

AERS data do have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive all adverse event reports that occur with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, AERS cannot be used to calculate the incidence of an adverse event in the U.S. population.



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

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

/s/

ALEKSANDER P WINIARSKI
09/27/2012

CAROL A HOLQUIST on behalf of JAMIE C WILKINS PARKER
09/27/2012
Signing on behalf of Jamie Wilkins Parket

KELLIE A TAYLOR
09/28/2012

CAROL A HOLQUIST
09/28/2012

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

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

Memorandum

Date: September 14, 2012

To: J. Christopher Davi, MS, Senior Regulatory Project Manager
Division of Anti-Infective Products

Eileen Navarro-Almario, MD, Lead Medical Officer
Division of Anti-Infective Products

From: Christine Corser, Pharm.D., Regulatory Review Officer
Division of Professional Drug Promotion

Subject: NDA #201688
TOBI[®] Podhaler[™] (tobramycin inhalation powder) hard capsules
for oral inhalation

As requested in your consult dated August 22, 2012, the Division of Professional Drug Promotion (DPDP) has reviewed the draft labeling for TOBI[®] Podhaler[™] (tobramycin inhalation powder) hard capsules for oral inhalation (TOBI Podhaler).

DPDP's, PI comments are based on the substantially complete version of the labeling titled, "TOBIplr22Aug12clean.doc" which was sent via email from Christopher Davi on August 22, 2012.

DPDP's comments are provided in the attached, clean version of the labeling. If you have any questions about DPDP's comments on the PI, please contact Christine Corser at 6-2653 or at Christine.Corser@fda.hhs.gov.

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

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

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

/s/

CHRISTINE G CORSER
09/14/2012

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

Memorandum

Date: February 12, 2012

To: J. Christopher Davi, MS, Senior Regulatory Project Manager, DAIP

From: Adora Ndu, Regulatory Review Officer, DCDP

Subject: NDA 201688
DCDP comments for TOBI® Podhaler™ (tobramycin inhalation powder)
hard capsules for oral inhalation
Patient Information (PPI) and Instructions for Use (IFU)

On August 22, 2012, DCDP received a consult request from DAIP to review the proposed PPI, and IFU for TOBI® Podhaler™ (tobramycin inhalation powder) hard capsules for oral inhalation.

DCDP has reviewed the proposed labeling using the following versions of the proposed labels received from DMPP on August 22, 2012, and August 28, 2012 respectively:

- TOBIplr22Aug12clean SCPI 08-22-12.doc
- tobramycin inhalation powder (TOBI Podhaler) 201688 DMPP PPI-IFU Marked AUG-2012.docx

After review of the proposed labeling, DCDP offers the following comments.

If you have any questions regarding the patient labeling, please contact Adora Ndu at 301-796-5114 or adora.ndu@fda.hhs.gov.

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

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

/s/

ADORA NDU
09/12/2012



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

NDA 201-688 – Regulatory Device Consult

Date: July 13, 2012

To: Mr. Christopher Davi, Regulatory Project Manager (OND/OAP/DAIOP)

From: Mr. Sugato De, M.S., Biomedical Engineer (ODE/DAGID/ARDB), Lead Reviewer

Applicant: Novartis Pharmaceuticals Inc.

Product Name: Tobii Podhaler

Indication: Management of chronic pulmonary infection due to *Pseudomonas aeruginosa* in patients with cystic fibrosis aged six years and older.

A. Executive Summary

In NDA 201-688, Novartis Pharmaceuticals has proposed a novel formulation of inhaled tobramycin powder (TBM100). The proposed powder is formulated via a proprietary PulmoSphere technology, a process designed to produce small porous particles that are intended to have significantly lower inter-particle cohesive forces than solid non-porous particles. This facilitates powder fluidization and dispersibility without the need to blend with larger carrier particles as in traditional dry powder formulation technology. The lack of lactose dilution and the gain in delivery efficiency commensurate with engineered particles enables a larger drug load and delivery of larger lung doses via dry powder inhalation.

Based on both the simulated flow rate study and the results of the Phase I clinical study a target fill mass of approximately (b) (4) was selected for Phase III clinical studies. Based on the mean Tobramycin content of the initial Phase III batches, the target fill mass was adjusted from (b) (4) to more accurately achieve the 28 mg dosage strength of Tobramycin in the capsule throughout the rest of Phase III. Instructions for use, as used throughout Phase III, require patients to take two inhalations per capsule, and should the patient see that the capsule did not empty completely on the first try; the patient is instructed to repeat the process for each capsule for a total of four inhalations. This addresses the potential for incomplete capsule emptying for patients with low inhaled volume (primarily young children). The final commercial dose is 112 mg Tobramycin (four 28 mg capsules), which is equivalent to (b) (4) of inhalation powder. The target delivered dose is 102 mg Tobramycin.

TBM100 inhalation powder is delivered by the T-326 Inhaler (TOBI Podhaler), 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. The capsule based system accommodates the high dose delivery requirements of TBM100 and provides improvements in convenience and quality of life relative to a jet nebulizer.

RECOMMENDATION: At this stage of review, the sponsor has provided a range of descriptive information for the proposed inhaler and detailed data that characterizes performance of the proposed device. Collectively, these tests are sufficient to demonstrate 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. Furthermore, the sponsor has provided a thorough assessment of mechanical safety and reliability for the proposed device. Accordingly, the information provided for review is adequate to provide a detailed in vitro analysis of the performance of the device component of the proposed combination product.

At the present time, the Center for Devices and Radiological Health (CDRH) considers the totality of biocompatibility testing provided for review insufficient. The Anesthesiology and Respiratory Devices Branch (ARDB) in CDRH considers devices that contact the patient gas pathway to be externally communicating devices with tissue contact. This is primarily due to the potential for chemical leachants from the device entering the patient's airway. Accordingly, the Branch recommends that biocompatibility testing be selected in accordance with ISO 10993-1 with careful consideration of the appropriate duration and level of contact of the device. Furthermore, it is recommended that the cumulative duration of use be considered in determining the duration of patient contact.

In accordance with the present version of ISO 10993-1, externally communicating devices with either prolonged (24 hours – 30 days) or permanent (>30 days) tissue contact require cytotoxicity sensitization, irritation or intracutaneous reactivity, systemic toxicity, subchronic toxicity, genotoxicity and implantation tests. As described in Section D below, the sponsor has provided acceptable test results in accordance with the aforementioned standard for cytotoxicity, sensitization, irritation and acute systemic toxicity. While these tests are the minimally accepted tests for prolonged contact with the mucosal membrane (the sponsor's categorization for the proposed device), these tests are not sufficient to validate biocompatibility for an externally communicating device with tissue contact.

If the Center for Drugs Evaluation and Research (CDER) agrees with ARDB's categorization of this device as an externally communicating device with tissue contact, then subchronic toxicity, genotoxicity, and implantation tests should be conducted by the sponsor. Please note that for externally communicating devices with tissue contact, the biocompatibility testing required for prolonged and permanent duration is equivalent. If the known extractables and leachables from the gas-pathway contacting components are below a threshold known to be associated with toxicity, then additional testing may not be necessary.

In addition, the Center for Devices and Radiological Health (CDRH) recognizes that there are a range of human factors and clinical efficacy concerns with the proposed product. Specifically, the human factors study results demonstrate patterns of failures, use errors and operational difficulties. These issues are expected to lead to modifications to product labeling and also user training. In addition, a number of these issues may reasonably lead to design changes that may affect the performance of the proposed device.

Given the totality of information that has been provided regarding the performance and use of the Tobi Podhaler, approval of the device cannot be recommended from a device-engineering standpoint.

B. Device Description

Overview:

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. The capsule based system accommodates the high dose delivery requirements of TBM100 and provides improvements in convenience and quality of life relative to a jet nebulizer.

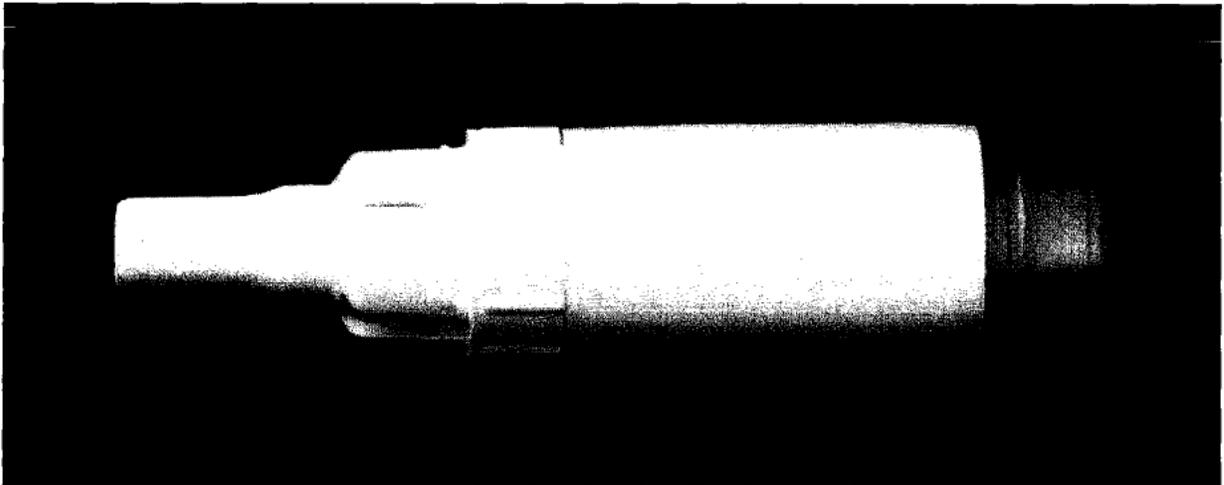


Figure 1: T-326 Inhaler (Tobi Podhaler)

No changes to the design have been made since the initiation of the TBM100 phase III clinical studies. The T-326 Inhaler is supplied to the patient in a case that protects the inhaler during shipment, storage and its one week in-use period. This case is made from the same plastic material as the inhaler.

Device Use:

To administer the drug, the patient inserts a single capsule containing the dry powder formulation into the device. The patient then manipulates the device to prepare for drug delivery. See Figure 2 below for a depiction of the components of the T-326 Inhaler.

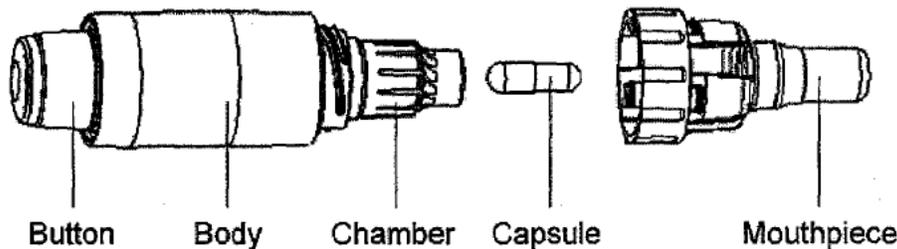


Figure 2: Parts of the T-326 Inhaler

TOBI Podhaler contains aluminum blister-packaged 28 mg TOBI Podhaler (tobramycin inhalation powder) clear, colorless hypromellose capsules with "NVR AVCI" in blue radial imprint on one part of the capsule and the Novartis logo in blue radial imprint on the other part of the capsule, and Podhaler inhalers.

Each Podhaler inhaler consists of the inhaler body, mouthpiece, capsule chamber and blue push button. The Podhaler inhaler is provided in a case that protects the device during shipment, storage and its one week in-use period. TOBI Podhaler capsules should always be stored in sealed blisters. Each TOBI Podhaler capsule should only be removed immediately before use.

The recommended dosage of TOBI Podhaler for both adults and pediatric patients 6 years of age and older is four 28 mg TOBI Podhaler capsules inhaled twice-daily for 28 days using the Podhaler inhaler. One dose requires inhaling the contents of four TOBI Podhaler capsules. Each dose of four capsules should be taken as close to 12 hours apart as possible; each dose should not be taken less than 6 hours apart.

Patients should be advised to complete a full 28-day course of TOBI Podhaler, even if they are feeling better. After 28 days of therapy, patients should stop TOBI Podhaler therapy for the next 28 days, and then resume therapy for the next 28 day on/28 day off cycle.

As described by the sponsor in DMF No. (b) (4) the end user is expected to complete the following steps in the course of therapy:

STEPS IN ONE INHALATION

- remove the Cap (if one is provided),
- remove the Mouthpiece,
- insert a Capsule,
- replace the Mouthpiece,
- invert the device (so that the Mouthpiece is facing downwards) and
- depress the Plunger by pressing on the Button at the end of the device until a hard stop is reached.
- release the Button
- the patient exhales to empty the lungs
- the patient places the mouthpiece into mouth past the teeth; being careful not block the mouthpiece with the tongue
- the patient inhales until their lungs feel full and if directed holds their breath
- once the patient has stopped inhaling the Mouthpiece can be removed from the mouth
- the Mouthpiece is removed from the inhaler, the Capsule discarded and the Mouthpiece and Cap (if one is provided) replaced.
- Repeat as needed to achieve desired dosing

In response to deficiencies raised by the FDA in a letter dated February 1, 2012, the sponsor provided further information with regards to the patient gas path and operational steps:

(b) (4)



Figure 4: Capsule Emptying in T-326 Inhaler

Mechanical Description:



The user then removes the capsule and discards it. The device may be re-used depending upon the target therapy requirements.

Device Components:

The following table from DMF No (b) (4) provides details on the component design for the T-326 Inhaler. The component name and a three-dimensional drawing are presented along with the component interface(s) and function.

Table 1: Components of T-326 Inhaler (Tobi Podhaler)

A large rectangular area of the page is completely redacted with a solid grey fill. In the top right corner of this redacted area, the text "(b) (4)" is printed in a small font.

2 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

C. Device Performance

Product Development:

During the production of the Phase III clinical batches, yield was sub-optimal and collectors with variable powder weights were observed. To resolve these issue three studies were performed:

- The first study was performed to replace the powder collection hardware (b) (4) [redacted].
- (b) (4) [redacted] to improve collection efficiency and uniformity.
- Finally, using a Quality by Design approach, (b) (4) [redacted], and a design space was identified to meet the critical quality attributes of the pivotal Phase III material. A set of designed experiments was undertaken to define the knowledge space of the spray drying process, and arrive at a design space that produced powder that met the specifications of the pivotal Phase III material. The resulting material was subsequently used in clinical trial C2303.



The knowledge space for the improved process, including operating points (blue dots) for pre-validation and validated stages are shown graphically in Figure 5 below:



Figure 5: Expansion of knowledge space of spray drying parameters for improved process.

The resulting batches were tested for water content, perflubron content, primary particle size, emitted dose, and aerodynamic particle size distribution. The response of these attributes to changes in the process parameters was statistically modeled.

A design space, which is within the knowledge space, was identified by using the established statistical models to predict where these attributes would meet acceptance criteria. Acceptance criteria for the bulk-powder properties and aerosol-performance metrics were calculated based on the Phase III and the improved process materials. The aerosol-performance metrics were considered to be the most important to match. Batches manufactured within the design space fulfilled the defined quality criteria.

The center-point operating condition was identified within the design space by requiring that the model predictions of the bulk-powder properties and aerosol-performance metrics met targets, which were based on the improved process experience only.

Review Synopsis: Subsequent to the manufacture of the Phase III clinical batches used in studies C2301 and C2302, improvements to the bulk powder manufacturing process were implemented to improve the physical stability of the emulsion and feedstock and reduce the yield variability and increase powder yield, commensurate with the needs of a commercial manufacturing process. Spray drying conditions were then optimized in order to produce powder with aerosol performance that matched that of the Phase III batches.

Following these improvements, the improved powder manufacturing process was transferred to commercial equipment of like design and validated. (b) (4). Spray drying ranges were confirmed to achieve aerosol performance comparable to the Phase III clinical batches. Drug product batches from the improved manufacturing process, both before and after transfer to the commercial equipment and subsequent validation, were used in clinical study C2303 requested by the Agency.

During the development work summarized above, the drug product composition and delivery device, the T-326 Inhaler, remained unchanged. Comparability data for Phase III and improved process batches are provided in the following sections.

Aerodynamic Particle Size Distribution (APSD):

APSD encompasses both the fluidization of powder from the delivery device (captured via delivered dose measurements) and deagglomeration of the powder. Therefore, APSD is considered the most relevant indicator of drug product aerosol performance and is commonly accepted as the most relevant metric that speaks to deposition of the inhaled powder in the lung. For this reason, APSD data were collected and used as the most relevant determinant of comparability of Phase III and improved process materials.

Figure 6 below shows the resultant APSD profiles. Eighteen batches manufactured using the Improved process (pre-validation and validated) were compared to the eighteen Phase III batches used in the clinical trials C2301 and C2302. Each data point is a mean of 5 measurements (1 capsule each) utilizing the Next Generation Impactor at 60 LPM.

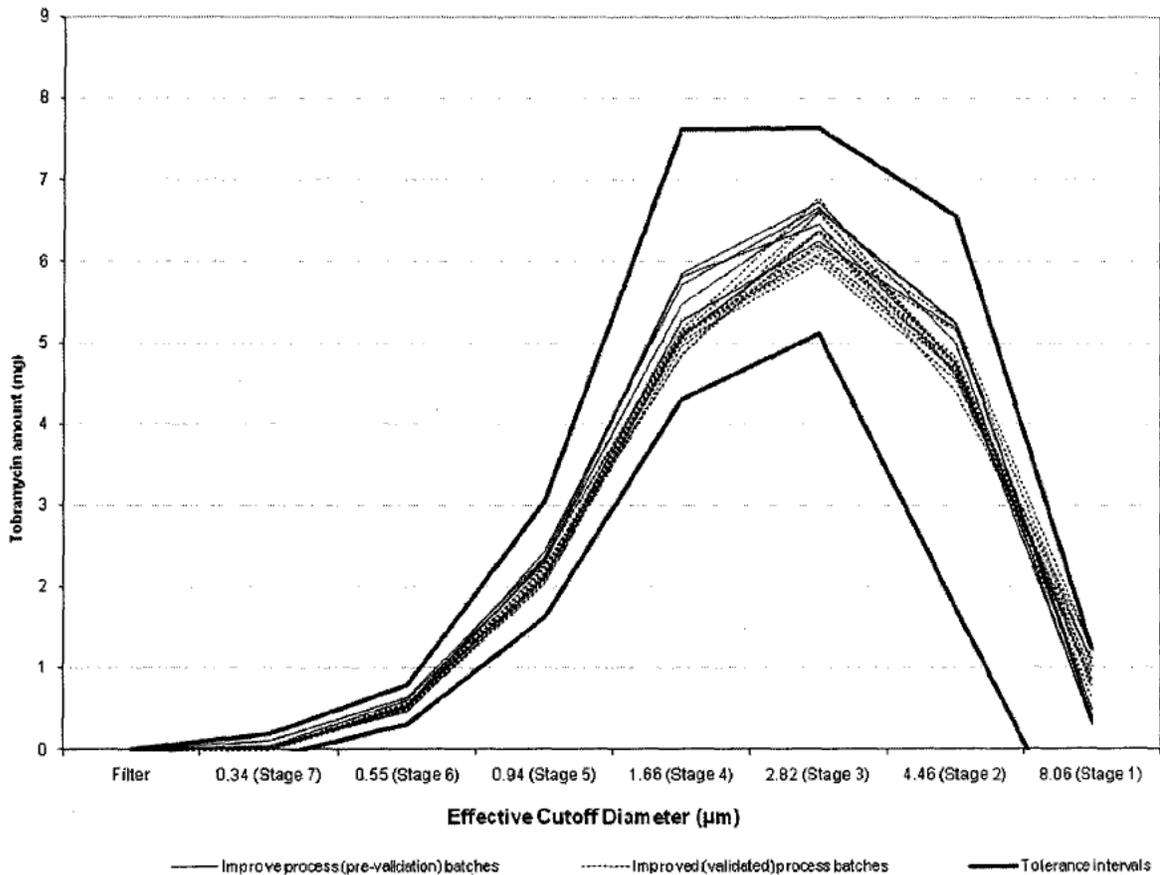
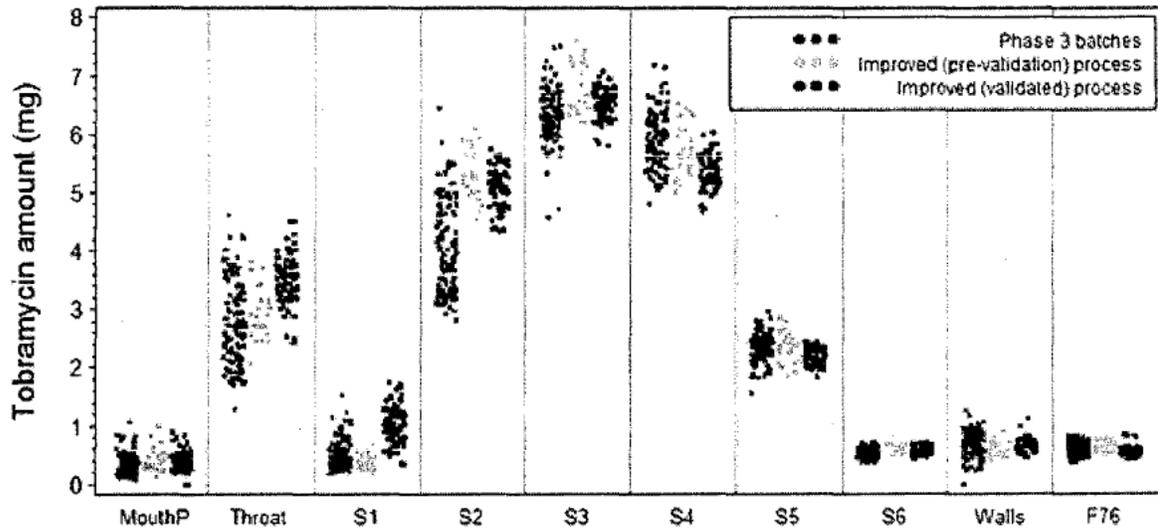


Figure 6: APSD: Phase III Improved (pre-validation) and Improved (validated) process batches.

Figure 7 shows stage by stage individual capsule data for Phase III, Improved (pre-validation) and improved (validated) process batches. This further demonstrates comparability related to the key aerosol attributes of the drug product discussed above. Almost without exception, the range of Phase III stage-by-stage aerosol data encompass those of both the Improved (pre-validation) and improved (validated) process batches.



Dots to the left represent APSD data (on individual capsule basis) of Phase 3 batches
 Dots in the middle represent APSD data (on individual capsule basis) of Improved (pre-validation) process batches
 Dots to the right represent APSD data (on individual capsule basis) of Improved (validated) process batches
 F76 Presents the sum of Filter + Stage 7 + Stage 6

Figure 7: Mass per stage for NGI release data at flow rate of 60 LPM.

Table 2 below displays stage by stage data for Phase III, Improved (pre-validation) and Improved (validated) process batches (grand mean and SD presented for each process) discussed above and further underlines comparability related to the key aerosol attributes of the drug product discussed above.

Table 2: Mass Per NGI Stage at Flow Rate of 60 LPM

	Tobramycin mass per stage (mg)									
	Mouth-piece Adapter	Throat	Stage 1	Stage 2	Stage 3	Stage 4	Stage 5	Stage 6	Stage 7	Filter
Aerodynamic cut-off diameter (μm)			≥ 8.06	≥ 4.46	≥ 2.82	≥ 1.66	≥ 0.94	≥ 0.55	≥ 0.34	< 0.34
Phase III process (mean value)	(b) (4)									
Min-Max										
SD (n=18)										
Improved (pre-validation) process (mean value)										
Min-Max										
SD (n=5)										
Mean difference										
Mean difference as a % of capsule content										
Improved (validated) process (mean value)										
Min-Max										
SD (n=13)										
Mean difference										
Mean difference as a % of capsule content										

Review Synopsis: As shown in the table above, the amounts of tobramycin deposited on the mouthpiece adapter and throat as well as Stage 1 and 2 were assessed for safety. The sums of all these components represent a particle size greater or equal to 4.46 μm . As it is commonly accepted that aerodynamic particle size of 5 μm is required for lung delivery the majority of the particles represented by throat, Stage 1 and Stage 2 can be considered non-respirable and are likely to be deposited in the oropharynx and subsequently swallowed. These differences in the results between the Phase III and Improved process lots are not expected to impact drug product safety due to the very low oral bioavailability of tobramycin (<1%).

With respect to the respirable portion, there are minimal differences in drug mass per stage for stages 5, 6 and 7 and Filter.

The small differences for stages 3 and 4 (ranging from (b) (4) of the capsule content, for the Improved (pre-validation) process, and (b) (4) of the capsule content for the Improved (validated) process) in comparison to the Phase III process are not of practical significance, particularly when one considers:

- the ranges and standard deviations around each of the means
- the small differences in absolute amounts of tobramycin relative to the mass of drug on the stage
- the encompassment of the Improved (pre-validation) and Improved (validated) process batch data by the Phase III batch data

Delivered Dose:

Delivered dose data were also collected to compare eighteen Phase III, and eighteen Improved process batches. For comparative purposes, the % label claim limits were fixed around the target delivered dose of 102 mg (4 capsules per dose) and results from this comparison are shown in Figure 8 and Table 3 below.

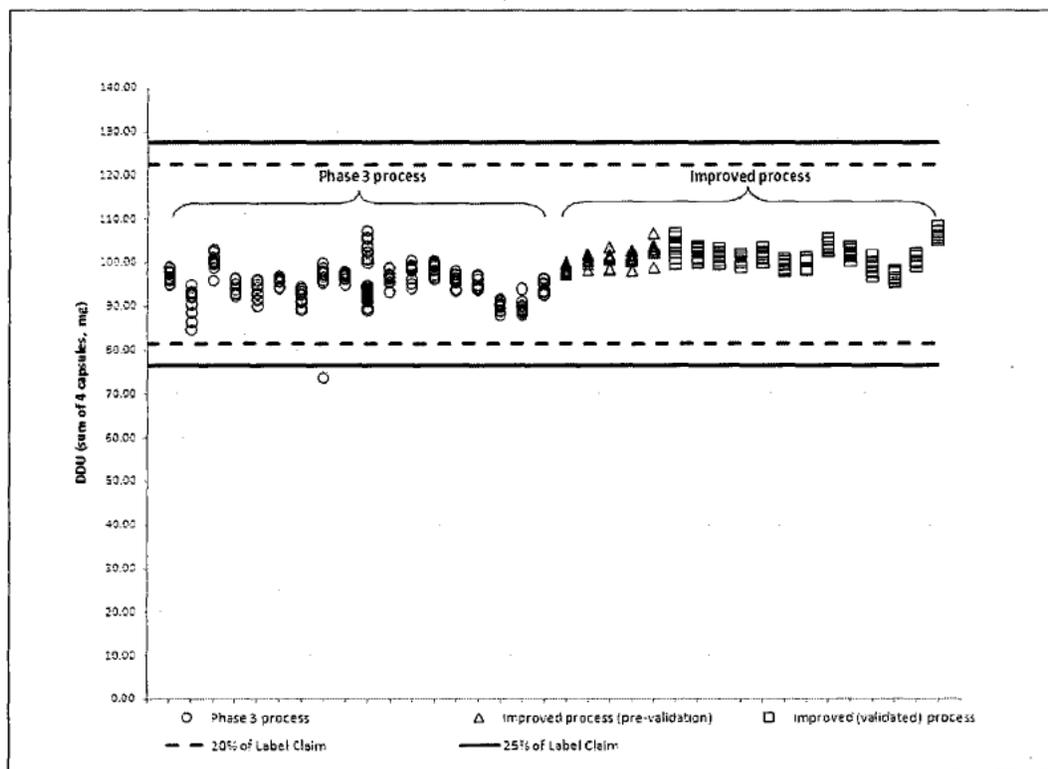


Figure 8: Delivered Dose Uniformity

Table 3: Delivered Dose (Means of Batch Release Data) (mg)

	Phase III (n = 18)	Improved (pre- validation) (n = 5)	Improved (validated) process (n = 13)
Mean	(b) (4)		
SD			
Range			
Grand mean (all processes)			
SD (all processes)			

Review Synopsis: All results met delivered dose testing requirements for uniformity as detailed in the sponsor’s test protocols. The mean delivered dose for the improved (pre-validation and validated) process batches are comparable with the Phase III process; (b) (4). The standard deviations for the doses are lower for the improved process compared to the Phase III process. In addition, the range of Phase III doses is within (b) (4) of the mean whereas for the improved processes, all doses were within (b) (4) of the respective means demonstrating an improvement in dose uniformity. Considering the nominal 102mg delivered dose of Tobramycin and the comparability of APSD testing, this very slight difference is unlikely to have clinical relevance.

Physical Characterization:

Multiple physical characterization techniques were used to compare the TBM100 inhalation powder of three batches manufactured using the Phase III, Improved (pre-validation), and Improved (validated) process, respectively.

The primary particle size distributions of bulk powder were determined by laser diffraction for Phase III and Improved process batches. The mean primary particle characteristics of (b) (4) cumulative undersize, respectively) are measured for each powder collector to verify process control.

The (b) (4) for powder produced from the improved (pre-validation and validated) process are (b) (4) than those of batches made using the Phase III process. The small differences in powder primary particle size were an anticipated consequence of the process improvements on emulsion stabilization and optimization of spray-drying conditions. These were required to obtain drug product with APSD performance equivalent to that of the Phase III batches while meeting the requirements of output and consistency commensurate with a commercial process. APSD is well-known and, as emphasized in regulatory guidance documents for aerosol products, commonly accepted as the most relevant size metric that speaks to deposition of the inhaled powder in the lung. There is no significant impact (b) (4) in primary particle size on APSD, (b) (4)

(b) (4)

(b) (4)



Figure 9: Primary particle size (b) (4) results for the Phase III, Improved (pre-validation) and Improved (validated) process batches.



○ Phase 3 △ Improved process (pre-validation) □ Improved (validated) process — Specification limit

Figure 10: Primary particle size (b) (4) results for the Phase III, Improved (pre-validation) and Improved (validated) process batches.

Phase III and Improved (pre-validation) batches bracket the final process batches with respect to (b) (4), respectively. Batches from all three processes were used in clinical studies.

Review Synopsis: Subsequent to Phase III process supplies (used in studies C2301 and C2302), manufacturing improvements were made in emulsion preparation and powder collection to enable more robust commercial manufacture. Throughout these improvements, the overall manufacturing process did not change. *In vitro* results show comparable aerosol delivery characteristics (e.g., mass per stage, delivered dose uniformity) of materials from each of the processes. Tolerance interval analysis of the APSD profiles presented demonstrates statistical comparability; therefore, tobramycin delivery to the lung is expected to be therapeutically equivalent for drug product produced from the Phase III process (used in studies C2301 and C2302) and the Improved (pre-validation and validated) process (used in study C2303).

D. Biocompatibility

As described in DMF No. (b) (4) biocompatibility testing for the proposed device was performed in accordance with the following:

- ISO 10993, Parts 1, 5, 10, “Biological Evaluation of Medical Devices”,
- FDA Blue Book Memorandum G95-1, “Use of International Standard ISO-10993, “Biological Evaluation of Medical Devices” and
- *USP Monographs*: <87>, “Biological Reactivity Tests, In Vitro” <88>, “Biological Reactivity Tests, In Vivo” and <1031>, “The Biocompatibility of Materials used in Drug Containers, Medical Devices, and Implants”.

This testing was performed on all Mucous Membrane and Drug Contacting components. The T326 Inhaler is categorized as “surface device, mucosal membrane contacting, limited duration (≤ 24 hour)” in accordance with provisions of the documents listed above. Upon consideration of cumulative device use over a patient’s lifetime it was decided that the testing performed on each component would be done to the level of a prolonged duration device (24 hours to 30 days).

For prolonged duration devices, ISO 10993 requires testing for Cytotoxicity, Sensitization and Intracutaneous Reactivity (or Irritation). The USP <1031> monograph indicates that for medical devices such as the T-326 Inhaler, in addition to the ISO 10993 testing requirements, a plastic material should meet the requirements of USP Class III (as described in USP <88>); this testing involves intravenous/intraperitoneal or intracutaneous injection of material extracts into mouse (acute systemic toxicity) or rabbit (intracutaneous reactivity) models, respectively. For primary device packaging components cytotoxicity testing was performed on those components made of materials different from the device (b) (4). The specific test methods selected for evaluating these parameters for the individual T-326 Inhaler and primary packaging components (b) (4) are summarized in Table 4 below:

Table 4: Summary of Biocompatibility Methods Used

Test Requirement	Test Performed	Method
Cytotoxicity	MEM Elution, L929 cells	ISO 10993, Part 5 (1999). Tests for In Vitro Cytotoxicity. 1X MEM extract.
Sensitization	Sensitization Study, guinea pig model	ISO 10993, Part 10 (2002). Tests for Irritation and Sensitization. Extraction vehicles used: Sodium chloride and sesame oil.
Intracutaneous Reactivity or Irritation	Vaginal Irritation Study ¹ , rabbit model	ISO 10993, Part 10 (2002). Tests for Irritation and Sensitization. Extraction vehicles used: Sodium chloride and sesame oil.
Acute systemic toxicity	Systemic Injection Test, mouse model	USP 27 <88> Class III. Extraction vehicles used for intravenous: Sodium Chloride and Alcohol in Saline 1:20. Extraction vehicles used for intra-peritoneal: Polyethylene glycol and sesame oil.

¹This study is a recognized alternative to the rabbit intracutaneous injection of material extracts.

The results of the biocompatibility tests that were performed are summarized in Table 5 below:

- **Cytotoxicity:** All test samples were evaluated as nontoxic and showed 0% cell lysis.
- **Sensitization:** All test samples showed no erythema and no edema and therefore no evidence of causing delayed dermal contact sensitization.
- **Irritation:** All test samples were evaluated as non-irritants.
- **Acute Systemic Toxicity:** There was no mortality or evidence of systemic toxicity from test samples prepared using extracts of the T-326 Inhaler components.

Table 5: Summary of Biocompatibility Methods Test Results

Component Name	Cytotoxicity Study	Sensitization Study	Vaginal Irritation Study	USP <88> Class III Systemic Toxicity
(b) (4)	No evidence of cell lysis or toxicity	No evidence of delayed dermal contact sensitization	Nonirritant	No mortality or evidence of systemic toxicity
	No evidence of cell lysis or toxicity	No evidence of delayed dermal contact sensitization	Nonirritant	No mortality or evidence of systemic toxicity
	No evidence of cell lysis or toxicity	No evidence of delayed dermal contact sensitization	Nonirritant	No mortality or evidence of systemic toxicity
	No evidence of cell lysis or toxicity	No evidence of delayed dermal contact sensitization	Nonirritant	No mortality or evidence of systemic toxicity
	No evidence of cell lysis or toxicity	No evidence of delayed dermal contact sensitization	Nonirritant	No mortality or evidence of systemic toxicity
	No evidence of cell lysis or toxicity	No evidence of delayed dermal contact sensitization	Nonirritant	No mortality or evidence of systemic toxicity
	No evidence of cell lysis or toxicity ¹	not applicable	not applicable	not applicable
	No evidence of cell lysis or toxicity ¹	not applicable	not applicable	not applicable

¹Met requirements of test based on representative component testing of Body, Mouthpiece and Guide

²Primary packaging components

Review Synopsis: At the present time, the Anesthesiology and Respiratory Devices Branch (ARDB) in the Center for Devices and Radiological Health (CDRH) considers devices that contact the patient gas pathway to be externally communicating devices with tissue contact. This is primarily due to the potential for chemical leachants from the device entering the patient’s airway. Accordingly, the Branch recommends that biocompatibility testing be selected in accordance with ISO 10993-1 with careful consideration of the appropriate duration and level of contact of the device. Furthermore, it is recommended that the cumulative duration of use be considered in determining the duration of patient contact.

In accordance with the present version of ISO 10993-1, externally communicating devices with either prolonged (24 hours – 30 days) or permanent (>30 days) tissue contact require cytotoxicity sensitization, irritation or intracutaneous reactivity, systemic toxicity, subchronic toxicity, genotoxicity and implantation tests (please reference Table 6 below). As described above, the sponsor has provided acceptable test results in

accordance with the aforementioned standard for cytotoxicity, sensitization, irritation and acute systemic toxicity. While these tests are the minimally accepted tests for prolonged contact with the mucosal membrane, these tests are not sufficient to validate biocompatibility for an externally communicating device with tissue contact.

If the Center for Drugs Evaluation and Research (CDER) agrees with ARDB's categorization of this device as an externally communicating device with tissue contact, then subchronic toxicity, genotoxicity, and implantation tests should be conducted by the sponsor. Please note that for externally communicating devices with tissue contact, the biocompatibility testing required for prolonged and permanent duration is equivalent.

If the known extractables and leachables from the gas-pathway contacting components are below a threshold known to be associated with toxicity, then additional testing may not be necessary.

Table 6: ISO 10993-1 (2009) Initial Evaluation Tests for Consideration

Device categorization by			Biologic effect								
nature of body contact (see 5.2)		Contact duration (see 5.3) A – limited (≤ 24 h) B- prolonged (>24 h to 30 d) C – permanent (> 30 d)	Cytotoxicity	Sensitization	Irritation or Intracutaneous reactivity	Systemic toxicity (acute)	Subchronic toxicity (subacute toxicity)	Genotoxicity	Implantation	Haemocompatibility	
Category	Contact										
Surface device	Intact skin	A	X	X	X						
		B	X	X	X						
		C	X	X	X						
	Mucosal membrane	A	X	X	X						
		B	X	X	X	O	O		O		
		C	X	X	X	O	X	X	O		
		Breached or compromised surface	A	X	X	X	O			O	
			B	X	X	X	O	O		O	
			C	X	X	X	O	X	X	O	
External communicating device	Blood path, indirect	A	X	X	X	X				X	
		B	X	X	X	X	O			X	
		C	X	X	O	X	X	X	O	X	
	Tissue/bone/dentin ⁺	A	X	X	X	O					
		B	X	X	X	X	X	X	X		
		C	X	X	X	X	X	X	X		
	Circulating blood	A	X	X	X	X			O [^]		X
		B	X	X	X	X	X	X	X	X	X
		C	X	X	X	X	X	X	X	X	X
Implant device	Tissue/bone	A	X	X	X	O					
		B	X	X	X	X	X	X	X		
		C	X	X	X	X	X	X	X		
	Blood	A	X	X	X	X	X	X	X	X	X
		B	X	X	X	X	X	X	X	X	X
		C	X	X	X	X	X	X	X	X	X

X = ISO Evaluation Tests for Consideration

O = These additional evaluation tests should be addressed in the submission, either by inclusion of the testing or a rationale for its omission.

Note + Tissue includes tissue fluids and subcutaneous spaces

Note ^ For all devices used in extracorporeal circuits

assembled device it was concluded that none of the compounds were present at levels that require further evaluation (e.g. leachables or toxicity studies). The controlled extraction studies served as a guide to develop routine extraction methods for the polypropylene materials.

Table 9: Range of Results ($\mu\text{g/g}$) From Semi-quantitative Controlled Extraction Studies



(b) (4)

(Continued on following page.)

The (b) (4) was refluxed in water:ethanol 50/50 (v/v), water:ethanol 90/10 (v/v), isopropanol and methylene chloride. Routine extraction was not required for the metal component, since there were not any extractables detected above the safety threshold.

E. Product Characterization

The following sections provide detailed information about characterization studies investigating the pharmaceutical performance of the drug product consisting of inhalation powder capsules delivered via the T-326 Inhaler. Table 10 summarizes the information from drug product characterizations provided in DMN No. (b) (4) in accordance with the Guidance for Industry on Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug products (Draft guidance 1998) that are applicable to the T-326 Inhaler.

Table 10: 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	Aerosol performance is affected at high humidity	Store inhaler in case, keep away from moisture. Use

Study	Section	Conclusions	Impact on Labeling
	4.3.10	conditions	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

Upon request by CDRH, the sponsor was asked to compare the range of product characterization studies performed in comparison to applicable clauses of IEC 60601-1. The information referenced in the response is as follows:

Table 11: Comparison of IEC 60601-1 to T-326 Inhaler Characterization

Test	IEC 60601-1 reference	T-326 inhaler test
Drop	§15.3.4.1 Specifies drop in 3 orientations from 1 m onto wood surface	T-326 Inhaler DVT Drop Test Dropped in 3 orientations at 3 temperature conditions (9 total drops per device) from height of 5' (~1.5 m) onto steel surface Passed function test at 95% confidence of 90% reliability
Push (Impact is not applicable to handheld device)	§15.3.2 Specifies application of a steady force of 250 N ± 10 N for a period of 5 s	T-326 Inhaler DVT Load Test Load of 90 lbf (~400 N) applied for 10s Passed function test at 95% confidence of 90% reliability
Stability	§9.4 Indicates that devices "intended to be placed on a surface such as a floor or a table shall not overbalance (tip over) or move unexpectedly."	The inhaler is not subject to this requirement based on its physical characteristics
Transportability	§3.130 Specifies that "equipment that is intended to be moved from one place to another whether or not connected to a	T-326 Inhaler DVT Physical Inspection T-326 Inhaler is 120 mm long x 31 mm in diameter T-326 Inhaler is 24 g

Test	IEC 60601-1 reference	T-326 inhaler test
Temperature	supply and without an appreciable restriction of range" §5.3 Specifies that "tests are performed within the range of environmental conditions."	T-326 Inhaler Thermal Shock Test 1. Inhalers stored at 50 °C for 4 hours 2. Inhalers stored at 0 °C for 4 hours Passed function test at 95% confidence of 90% reliability
Leakage	§13.2.6 Specifies that devices shall be "so constructed that liquid that might escape in a single fault condition does not result in an unacceptable risk."	Not relevant to this device – no liquid stored
Humidity preconditioning	§5.7 20 °C – 32 °C / 93% RH for 48 h	T-326 Inhaler DVT Extreme Storage Test 4 day test, with 25 steps, cycling between extremes -20 °C / 20% RH and 50 °C / 90% RH Passed function test at 95% confidence of 90% reliability
Cleaning	§11.6.6 Specifies that devices shall be "capable of withstanding, without damage or deterioration of safety provisions, the cleaning or disinfection PROCESSES specified in the instructions for use."	Cleaning study test report

Table 3-2 Additional information on T-326 inhaler reliability

Test	Purpose	T-326 inhaler test
§15.3.7 Environmental influences	Evaluate device performance after extended real-time storage (ageing) at specified conditions	T-326 Inhaler Development stability report
§15.3.7 Environmental influences	Evaluate device performance after exposure to shock and vibration simulating normal transportation conditions	Report for distribution study of Tobramycin Inhalation Powder (TBM100C) in the revised commercial kit configuration
§9.5 - Expelled parts	Evaluate device resistance hazards caused by loose parts resulting from unintentional disassembly or intentional disassembly without the use of tools	T-326 DVT Disassembly Force Tests Linear force of minimum 10 lbf (~40 N) applied to disassemble device plunger and button Passed at 95% confidence of 90% reliability

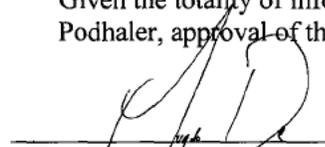
F. Review Conclusions and Recommendation

At this stage of review, the sponsor has provided a range of descriptive information for the proposed inhaler and detailed data that characterizes performance of the proposed device. Collectively, these tests are sufficient to demonstrate that the Tobi Podhaler reliably delivers the target delivered dose with a mass-median aerosol diameter (MMAD) between (b) (4) over the range of batch formulations studied. Furthermore, the sponsor has provided a thorough assessment of mechanical safety and reliability for the proposed device. Accordingly, the information provided for review is adequate to provide a detailed in vitro analysis of the performance of the device component of the proposed combination product.

At the present time, the Center for Devices and Radiological Health (CDRH) considers the totality of biocompatibility testing provided for review insufficient. The Anesthesiology and Respiratory Devices Branch (ARDB) in CDRH considers devices that contact the patient gas pathway to be externally communicating devices with tissue contact. This is primarily due to the potential for chemical leachants from the device entering the patient's airway. Accordingly, the Branch recommends that biocompatibility testing be selected in accordance with ISO 10993-1 with careful consideration of the appropriate duration and level of contact of the device. Furthermore, it is recommended that the cumulative duration of use be considered in determining the duration of patient contact.

In accordance with the present version of ISO 10993-1, externally communicating devices with either prolonged (24 hours – 30 days) or permanent (>30 days) tissue contact require cytotoxicity sensitization, irritation or intracutaneous reactivity, systemic toxicity, subchronic toxicity, genotoxicity and implantation tests. As described in Section D below, the sponsor has provided acceptable test results in accordance with the aforementioned standard for cytotoxicity, sensitization, irritation and acute systemic toxicity. While these tests are the minimally accepted tests for prolonged contact with the mucosal membrane (the sponsor's categorization for the proposed device), these tests are not sufficient to validate biocompatibility for an externally communicating device with tissue contact. If the Center for Drugs Evaluation and Research (CDER) agrees with ARDB's categorization of this device as an externally communicating device with tissue contact, then subchronic toxicity, genotoxicity, and implantation tests should be conducted by the sponsor. Please note that for externally communicating devices with tissue contact, the biocompatibility testing required for prolonged and permanent duration is equivalent. If the known extractables and leachables from the gas-pathway contacting components are below a threshold known to be associated with toxicity, then additional testing may not be necessary.

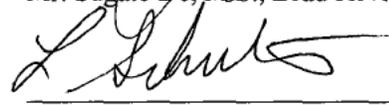
In addition, the Center for Devices and Radiological Health (CDRH) recognizes that there are a range of human factors and clinical efficacy concerns with the proposed product. Specifically, the human factors study results demonstrate patterns of failures, use errors and operational difficulties. These issues are expected to lead to modifications to product labeling and also user training. In addition, a number of these issues may reasonably lead to design changes that may affect the performance of the proposed device. Given the totality of information that has been provided regarding the performance and use of the Tobi Podhaler, approval of the device cannot be recommended from a device-engineering standpoint.



Mr. Sugato De, M.S., Lead Reviewer

8/24/12

Date



Dr. Lex Schultheis, ARDB Branch Chief

8/24/12

Date



Dr. Tejashri Purohit-Sheth, Clinical Deputy Director

8/27/12

Date

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

/s/

JOSEPH C DAVI

08/29/2012

This review is being placed in DARRTS on behalf of the CDRH device reviewer.

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

PATIENT LABELING REVIEW

Date: **August 28, 2012**

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

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

From: Shawna Hutchins, MPH, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

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

Drug Name (established name): TOBI Podhaler (tobramycin inhalation powder)

Dosage Form and Route: Hard Capsules for Oral Inhalation

Application Type/Number: NDA 201-688

Applicant: **Novartis Pharmaceuticals Corporation**

1 INTRODUCTION

On December 21, 2011, Novartis Pharmaceuticals Corporation submitted for the Agency's review a New Drug Application (NDA 201-688) for TOBI Podhaler (tobramycin inhalation powder) an aminoglycoside antibacterial indicated for the management of cystic fibrosis patients with *pseudomonas aeruginosa*. On January 03, 2012, the Division of Anti-Infective Products (DAIP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for TOBI Podhaler (tobramycin inhalation powder).

This review is written in response to a request by DAIP for DMPP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for TOBI Podhaler (tobramycin inhalation powder).

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU will be forthcoming.

2 MATERIAL REVIEWED

- Draft TOBI Podhaler (tobramycin inhalation powder) PPI and IFU received on December 21, 2011 and received by DMPP on August 22, 2012.
- Draft TOBI Podhaler (tobramycin inhalation powder) Prescribing Information (PI) received on December 21, 2011, revised by the Review Division throughout the review cycle, and received by DMPP on August 22, 2012.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI and IFU the target reading level is at or below an 8th grade level.

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

In our review of the PPI and IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI and IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

- The enclosed IFU review comments are collaborative DMPP and DMEPA.

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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



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

/s/

SHAWNA L HUTCHINS
08/28/2012

MELISSA I HULETT
08/28/2012

LASHAWN M GRIFFITHS
08/28/2012

8/24/2012

MANDATORY: Send a copy of the consult request form to the Office of Combination Products (OCP) as follows:

- Originating Center: When the consult request is initiated.
- Consulting Center: When the consult is completed.

Email: combination@fda.gov or FAX: 301-847-8619

For additional information: Contact OCP by email or by telephone (301-796-8930) or refer to OCP's intranet page <http://inside.fda.gov:9003/ProgramsInitiatives/CombinationProducts/ReviewerTools/default.htm>.

For Consulting Center Use Only:

Date Received: 1/3/2012
Assigned to: Quynh Nhu Nguyen
Date Assigned: _____
Assigned by: _____
Completed date: 8/22/2012
Reviewer Initials: QNN
Supervisory Concurrence: Ron Kaye

Intercenter Request for Consultative or Collaborative Review Form

To (Consulting Center):

Center: Office of Combination Products
Division: ARDP
Mail Code: HF
Consulting Reviewer Name: Ron D. Kaye
Building/Room #: WO 66; Room 2520
Phone #: (301) 796-6289
Fax #: _____
Email Address: _____
RPM/CSO Name and Mail Code: _____

From (Originating Center):

Center: Center for Drug Evaluation and Research
Division: Division of Anti-Infective Drug Products
Mail Code: HF-520
Requesting Reviewer Name: Shrimant Mishra, MD
Building/Room #: WO 22, Room 6209
Phone#: (301) 796-2301
Fax #: _____
Email Address: _____
RPM/CSO Name and Mail Code: J. Christopher Davi, Sr. RPM
Requesting Reviewer's Concurring Supervisor's Name: Eileen Almario Navarro, MD

Receiving Division: If you have received this request in error, you must contact the request originator by phone immediately to alert the request originator to the error.

Date of Request: January 3, 2012

Requested Completion Date: August 24, 2012

Submission/Application Number: 201,688
(Not Barcode Number)

Submission Type: NDA
(510(k), PMA, NDA, BLA, IND, IDE, etc.)

Type of Product: Drug-device combination Drug-biologic combination Device-biologic combination
 Drug-device-biologic combination Not a combination product

Submission Receipt Date: December 21, 2011

Official Submission Due Date: October 19, 2012

Name of Product: TOBI Podhaler (tobramycin inhalation powder)

Name of Firm: Novartis Pharmaceuticals Corporation

Intended Use: TOBI Podhaler (tobramycin inhalation powder) is indicated for the management of cystic fibrosis patients with Pseudomonas aeruginosa.

Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate):

This NDA is an electronic submission located in DARRTS under NDA 201,688 as supporting document #1. In addition, a CD-rom of the pertinent NDA sections has been provided, as well a paper copy of the pertinent sections of the NDA submission. A sample device (T-326 Podhaler) and blister card (capsules) to be used in conjunction with the device will also be provided.

Documents to be returned to Requesting Reviewer? Yes No

Complete description of the request. Include history and specific issues, (e.g., risks, concerns), if any, and specific question(s) to be answered by the consulted reviewer. The consulted reviewer should contact the request originator if questions/concerns are not clear. Attach extra sheet(s) if necessary:

Type of Request: Consultative Review Collaborative Review

Please provide a review focusing on the human factors aspect of this drug-device combination.

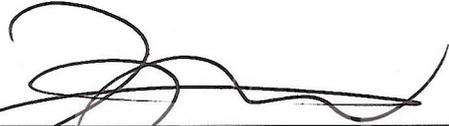


Food and Drug Administration
Office of Device Evaluation
10903 New Hampshire Avenue
Silver Spring, MD 20993

DATE: August 22, 2012

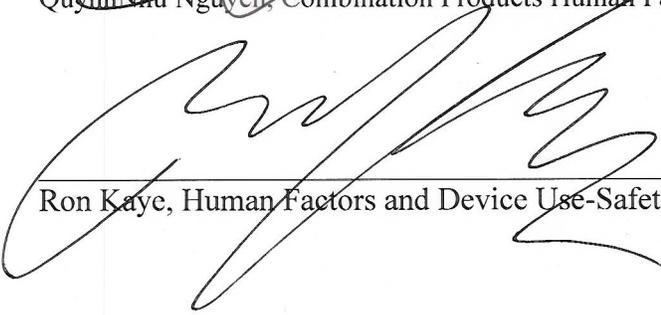
FROM: QuynhNhu Nguyen, Biomedical Engineer/Human Factors Reviewer, CDRH/ODE/DAGID
THROUGH: Ron Kaye, Human Factors and Device Use-Safety Team Leader, CDRH/ODE/DAGID
CC: Molly Story, Human Factors and Accessible Medical Technology Specialist, DAGID
TO: Christopher Davi, Regulatory Project Manager, CDER/OND/OAP/DAIP

SUBJECT: **NDA 201688**
Applicant: Novartis
Device Constituent: Tobi T-326 Inhaler
Drug Constituent: Tobi
(indicated for the management of cystic fibrosis patients with Pseudomonas aeruginosa)
Intended Treatment: Cystic Fibrosis



QuynhNhu Nguyen, Combination Products Human Factors Specialist

8/22/2012
Date



Ron Kaye, Human Factors and Device Use-Safety Team Leader

8/22/2012
Date

Contents

OVERVIEW AND CDRH HUMAN FACTORS RECOMMENDATIONS.....	3
REVIEW MATERIALS	5
CDRH HUMAN FACTORS REVIEW	5
COMBINATION PRODUCT DEVICE INFORMATION	5
CDRH HUMAN FACTORS INVOLVEMENT HISTORY.....	5
REVIEW OF HUMAN FACTORS RELATED INFORMATION	5
<i>Device Description</i>	5
<i>User Interface and Use Interaction</i>	6
<i>Proposed Intended Users</i>	6
<i>Proposed Intended Use</i>	7
<i>Intended Use Environments</i>	7
<i>Study Design</i>	7
<i>Expected Training and Realistic Use of Instructions for Use (IFU)</i>	7
<i>User Task and Use-Related Risks Analysis, Characterization, and Prioritization</i>	7
<i>Summary of Validation Human Factors Study Results</i>	8
<i>Detailed Evaluation of Human Factors/Usability Results</i>	9
<i>Discussion and Implications for Additional Risk Mitigation</i>	10

CDRH Human Factors Review

Overview and CDRH Human Factors Recommendations

The Division of Anti-Infective Products, Office of Antimicrobial Products, Office of New Drugs, Center for Drugs Research and Evaluation, requested a Human Factors consultative review of the NDA 201688 submitted by Novartis. This review provides CDRH's review and recommendations on the Human Factors related information contained in the NDA specifically the TOBI Podhaler (T-326 inhaler) Usability Evaluation, Final Report, Document Reference # 8932 0013b, dated 23-Nov-2011.

The Human Factors study results showed patterns of failures, use errors, and operational difficulties, which indicated that the device user interface and its labeling including instructions for use and package insert and training materials are not optimized for safe and effective use. Therefore, this reviewer recommends that the proposed product "not approvable" unless additional improvements to the device, its labeling, and training have been implemented and additional human factors testing demonstrates that demonstrate that representative uses can safely and effectively use the device without any pattern of use errors or operational difficulties. The following text (in blue) can be transmitted to Novartis.

1. Your Human Factors study results showed patterns of failures, use errors, and operational difficulties. In response to these findings you stated that you will modify the Instructions for Use, and the user training. This review agrees with your conclusion that the results of your studies indicate that modifications are necessary. However you have not provided rationale to support your conclusion that IFU and training modifications are sufficient or appropriate mitigations, nor have you described either the weaknesses you believe exist in the current IFU nor the specific improvements you intend to make. Also, you have not shown results of subsequent evaluation that demonstrate the effectiveness of those improvements and have provided no rationale for why these modifications would be preferable to modifications to the design of your device. Please provide these clarifications and additional information.
2. Your testing reported more than half of the users did not look at the IFU and package insert although you state that improvements to the IFU will be made to improve the performance of users. This review finds that the importance of reading the IFU should be stated clearly on the cover of that document so that the user's attention is caught by it immediately without opening and reading it. As with other mitigations for use errors identified by prior testing, subsequent testing should provide evidence that this modification impacts user behavior.
3. The need for training should be clearly stated in the physician and user instructions and package insert.
4. Because pediatric users were unable to use the device effectively, instructions and training should direct caregivers/providers to set up the device.
5. With the extent of problems users had with orienting the capsule and the force required to pierce it, you should consider modification to the design to improve performance on these critical tasks.

6. All patterns of use failures should be considered with respect to the associated components in your user training and IFU with the intent to reduce performance the performance failures you found in your Usability testing.
7. When you perform additional testing to demonstrate the adequacy of your mitigation efforts, please ensure that you include representative users, prioritize the testing in accordance with the potential clinical impact of use error and includes adequate subjective assessment from study participants so that any errors that do occur can be understood in terms of their cause from the perspective of the users. Residual risk associated with use that cannot be further reduced through modifications of training, labeling, or modifications to the design of the UI should be discussed and rationale provided for why it cannot be further reduced. Note that stated plans to modify design flaws that could result in clinical impact on patients in future versions of the device are generally unacceptable.

Guidance on human factors procedures to follow can be found in *Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management*, available online at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094460.htm>. Note that we recently published a draft guidance document that, while not yet in effect, might also be useful in understanding our current thinking and our approach to human factors. It is titled, *Applying Human Factors and Usability Engineering to Optimize Medical Device Design* and can be found online at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259748.htm>

Review Materials

DARRTS/EDR:

Sequence 0000, Section 5.3.5.4

Study Report on US users

IR Request Responses dated 26-Jun-2012, and 23-Jul-2012

CDRH Human Factors Review

Combination Product Device Information

Submission Number: NDA 201699

Applicant: Novartis

Drug Constituent: Tobramycin (inhalation powder)

Device Constituent: Tobi T-326 Inhaler

Intended treatment: Cystic Fibrosis

CDRH Human Factors Involvement History

- 30-JAN-2012: CDRH HF was requested to provide a consultative review of a report for a final Human Factors/usability validation (summative) study

Review of Human Factors Related Information

Device Description

The TOBI T-326 podhaler is a handheld inhaler used to deliver Tobramycin, an inhalation powder contained in a blister capsules, used to treat Cystic Fibrosis. Blistered capsules are delivered in a weekly pack that contains the necessary doses for one week and one inhaler in its case. A monthly patient pack contains four weekly packs and one reserve inhaler in its case. A full dose consists of 4 capsules. Patients are instructed to inhale the contents of 4 capsules in the morning and 4 capsules in the evening.

The Podhaler is manually operated, breath-activated, unit-dose dry-powder inhaler. 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.



Figure 1: Unlabeled Podhaler

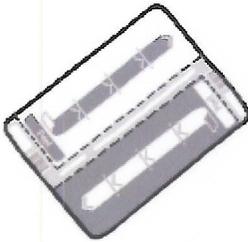


Figure 2: Blister Card

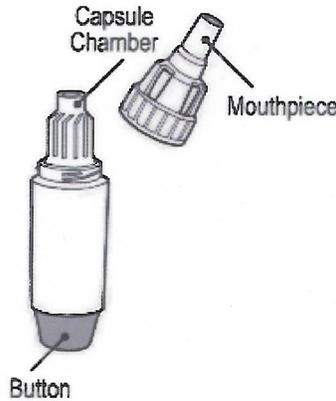


Figure 3: Inhaler and Components

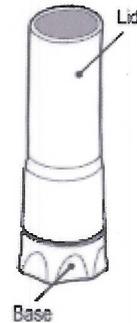


Figure 4: Storage Case

User Interface and Use Interaction

Before initial use, a user:

- Removes the Podhaler from its case by holding the base and twisting off the cover in a counter-clockwise direction.
- Stands the Podhaler upright in the base of the case
- Unscrews the mouthpiece in a counter-clockwise direction
- Takes one blister card and tear the perforations along the length and then width
- Peels the foil from the blister card to reveal one capsule
- Places the capsule into the inhaler chamber
- Puts the mouthpiece back on
- Screws the mouth piece on until it stops
- To pierce the capsule, holds the inhaler with the mouthpiece pointing down and presses the blue button firmly with the thumb
- Places mouth over the mouthpiece and make a tight seal
- Inhales deeply with a single breath
- Removes the inhaler from mouth and holds breath for 5 seconds
- Takes the second breath
- Repeats all steps to deliver all four capsules to receive a complete dose
- Once a complete dose has been delivered, puts the mouthpiece back on
- Wipes the mouthpiece with a clean/dry cloth
- Places the inhaler back in the storage case
- Twists the cover clockwise until it is closed tightly.

Proposed Intended Users

The user population is comprised of patients who either have a clinical diagnosis of cystic fibrosis, or have personal characteristics representative of cystic fibrosis (but not necessarily a clinical diagnosis of cystic fibrosis). There are four distinct user groups identified and recruited for the study

- Younger children (age 6-8), 16 participants
- Older children (age 9-12), 15 participants
- Teenagers (age 13-17), 15 participants
- Adults (age 18+), 16 participants

All study participants either had a clinical diagnosis of cystic fibrosis (n=12), or of asthma (n=50). Please note that since Novartis intends to market this product in the US, and while the report presented data for both EU and US participants, this reviewer only focused on study results of US participants.

Proposed Intended Use

TOBI Podhaler is an aminoglycoside antibacterial indicated for the management of cystic fibrosis patients with *Pseudomonas aeruginosa*.

Intended Use Environments

The Podhaler is intended to be used in the home. Therefore, the validation study included a “take-home” study stage, which was intended to investigate the device use in the home environment. 34 participants or participants/caregivers participated in this stage.

Study Design

The study is divided into three distinct phases:

1. Interviews were conducted with HCP to determine level of training required for use with the device
2. A pilot study was conducted to rehearse the study protocol
3. A main usability was conducted where patients and caregivers were required to:
 - a. Participate in an initial interview and training session, which was followed by an observed assessment of first inhaler use
 - b. Participate in a five day at home use where morning and evening doses were simulated using commercial weekly patient packs with empty inhalation capsules
 - c. Participate in the final interview with a final observed assessment of use followed by participant debriefing

Expected Training and Realistic Use of Instructions for Use (IFU)

Analysis conducted by Novartis indicated that all Cystic Fibrosis patients would receive training from their Healthcare Provider (HCP). As a result, Novartis provided representative training to all study participants. However, the specific content and duration were not specified in the study report. In addition, the participants were not forced to read the IFU but were informed that it is available.

User Task and Use-Related Risks Analysis, Characterization, and Prioritization

A use-related risks analysis could not be found in the original submission, and therefore, the reviewer was unclear on the rationale on the task selection, and task priority for the study. Novartis responded on 26-June-2012 to an Information Request (IR) letter requesting information on risk-analysis and task selection and prioritization for the study. In this response, Novartis referred to a document titled “Inhaler HFE/UE Summary Report” reference # T-326-TBM100. Section 5 of this document discussed the identification of critical tasks and their selection for evaluation in the validation study. The potential use errors of critical tasks identified were grouped into clusters

according to the IFU steps to which they applied. For example, a Subject piercing the inhalation powder hard capsule multiple times by repeatedly pressing the Device button would be categorized under the cluster: ‘Capsule piercing.’ As a result, Novartis identified five separate clusters of critical tasks as follows:

Table 1: Critical Tasks for Use with Inhaler

ID	Category	Descriptions	IFU use steps
A	Cluster 1	Setup, load capsule	(b) (4)
B	Cluster 2	Capsule piercing	
C	Cluster 3	Inhalation technique	
D	Cluster 4	Check procedure, full dose taken	
E	Cluster 5	Clean and store	
F	General misuse	General misuse	

In this section, Novartis also provided the following definition for use performance: A ‘systematic’ failure is defined as a failure which occurs on all instances of a particular step in the user’s dosing process required for the inhalation of a complete dose (4/4 capsules).

Summary of Validation Human Factors Study Results

For task performance, the study results show that:

- First attempt phase - immediately after training and before the in-home use segment (n=62)
 - 9 subjects/subject pairs did not complete a successful dosing on the first attempt
 - 58 subjects/subject pairs completed a successful dosing procedure with 3 of the 4 capsules.
 - 61 subjects expressed understanding that a complete dose comprises of 4 capsules
- Final interview - 1 week after first attempt use (n = 34)
 - 32 subjects or subject/caregiver pairs demonstrated successful dosing with 4 capsules
 - 34 subjects/subject pairs completed a successful dosing procedure with 3 of the 4 capsules

In order to fully evaluate the study results, and understand the significance of use-errors that were identified in the study, Novartis was asked to submit an analysis of residual risk of the use failures/errors identified in the study to determine if additional design and/or labeling modifications are indicated or if not, and this analysis should also address the possibility or practicality of reducing these risks further and address whether the residual risk is outweighed by the advantages offered by the device.

Novartis provided a response on 26-June-2012, which referenced to a document titled “Inhaler HFE/UE Summary Report” (document reference # T-326-TBM100). This document provided in Table 7-6 Novartis’ analysis of critical use errors and in Table 7-10 Novartis’s analysis of subjective feedback from test participants on failures and difficulties. The use errors analysis were not clear on the root cause of all of the use errors but it identified additional risk mitigations which included some IFU changes and more emphasis in the recommended training process although these recommendations were not specified. Subjective data indicated that users experienced many difficulties and confusion while administering a simulated dose including now knowing what a fully pierced capsule look like and not understanding the importance of piercing orientation. Other

difficulties were related to product design of the blister package. Pediatric patients reported that they experienced difficulty in depressing the button on the inhaler.

Detailed Evaluation of Human Factors/Usability Results

Novartis was requested to provide additional analysis on the use errors by individual participants or participant pairs and stratified by age.

First Time Use Results

Of the total of the first time use study participants (n=32), there were 48 pediatric participants (under the age of 21), and 15 adult participants (above the age of 21). Of the 48 pediatric participants, there were only two participants (age = 17) who were not paired with a caregiver/family member i.e. they performed study tasks independently. The other 46 pediatric participants were reported to receive assistance/intervention from caregivers while performing tasks. The numbers of participants received assistance/intervention from caregivers varied across all user tasks.

In summary, 21 pediatric participants (44%) committed at least one use errors to a total of 11 use errors while attempting to deliver a simulated dose. The amount of critical use errors committed varies across all subgroups within the pediatric participants. For the adult participants, five participants (33%) committed at least one use errors to a total of seven use errors while attempting to deliver a simulated dose. Similar to the pediatric group, the amount of critical use errors also varies across all participants. The following list provides a summary of notable use errors that had relatively high frequency for both pediatric and adult participants:

- 39 (63 %) subjects did not refer to the IFU
- 35 (56 %) subjects did not exhale fully prior to inhalation at least once
- 20 (32 %) subjects did not correctly orient the device while piercing capsules at least once
- 20 (32 %) subjects failed to remove and check the capsule to determine if that capsule is pierced at least once
- 17 (27 %) subjects did not inhale twice from at least one capsule
- 13 (21 %) subjects did not clean the mouthpiece
- 8 (13 %) subjects depressed the button incorrectly (more than once)

Overall, the study results indicated that while there were relatively high number of errors committed by test participants across all age groups, only nine participants failed to deliver a dose successfully (8 pediatric participants and 1 adult participant) during their first time use. It should be noted that all 8 pediatric participants were paired with their caregivers. The use errors committed by these nine participants were reviewed in detail to determine if there was a trend in either the same type of errors committed by all participants or the same frequency of errors committed that could impact successful delivery. However, the types of errors and the frequency of error commission varied across all participants. In terms of the frequency, the two most frequent errors (44%, 4 out of 9 participants) were in correct device orientation while piercing, and inhaling twice from each capsule. The next frequent errors (33%, 3 out of 9 participants) were due to unpierced capsule, blowing into the device, and not properly cleaning the device. (Reference: First Time Use Table, page 65).

Post 1-Week Use Evaluation Results

Of the total of the post 1-week time use study participants (n=34), there were 26 pediatric participants and eight adults participants. Of the 26 pediatric participants, there was only one participants (age = 21) who was not paired with a caregiver/family member i.e. they performed study tasks independently. The other 25 pediatric participants were reported to receive assistance/intervention from caregivers while performing tasks. The numbers of participants received assistance/intervention from caregivers varied across all user tasks.

In summary, 23 pediatric participants (88%) committed at least one use errors to a total of 6 use errors while attempting to deliver a simulated dose. The amount of critical use errors committed varies across all subgroups within the pediatric participants. For the adult participants, eight participants (100%) committed at least one use errors to a total of 5 use errors. Similar to the pediatric group, the amount of critical use errors also varies across all participants. The following list provides a summary of notable use errors that had relatively high frequency for both pediatric and adult participants:

- 22 (65 %) subjects did not exhale fully at least once prior to inhalation
- 17 (50 %) subjects did not remove and check the capsule to ensure it is pierced at least once
- 15 (44 %) subjects did not correctly orient the device while piercing capsules
- 9 (26 %) subjects did not clean the mouthpiece

Overall, two participants (1 pediatric participant and 1 adult participant) were reported to fail to deliver a dose successfully during their post 1-week use.

Capsule Inspection Test

A separate capsule inspection test was conducted to evaluate participant's ability to assess how much powder remained in the capsule and to determine whether they need to re-inhale. The study participants (n=62) were presented with capsules with different powder fill volumes after use scenario instead of during use, and their results were:

- 17 subjects (27%) decided to re-inhale a completely empty capsule with normal trace powder
 - 1 subject (2%) decided not to re-inhale capsule with 1/3 fill
 - 6 subjects (10 %) decided not to re-inhale capsule with 2/3 fill or completely full.
- These full or 2/3 full capsules confused subjects and subjects assumed that either the capsule or device was defective and would call physician and change to spare inhaler.

The capsule inspection testing demonstrated that users experienced some confusions on when they need to re-inhale.

Discussion and Implications for Additional Risk Mitigation

The study report showed that while the number of participants decreased from first use to post 1-week use (n=62 to n=34), there was a relatively higher number of participants committing use errors in the post 1-week use assessment as shown in table 2 :

Table 2: Comparison between First Time Use and Post 1-Week Use

	First Time Use (n=62)	Post 1-Week Use (n=34)
# of Pediatric Participants Committed Use Errors	21	23
# of Adult Participants Committed Use Errors	5	8

In addition, of the 34 participants who completed the entire Human Factors study, eight participants (6 pediatric participants and 2 adult participants) committed more use errors in the post 1-week use compared to first time use. These results indicated that use performance did not improve even when the participants were exposed to multiple opportunities to use the device. Additionally, participants were not able to apply the information that they learned from the training.

While Novartis attempted to provide an analysis of subjective feedback obtained from test participants, this analysis did not appear to provide complete follow-up discussions on all failures. However, it did identify numerous issues where participants did not understand key principles for using the device, as well as, numerous confusions and use difficulties. For example, participants either:

- did not know what a pierced capsule should look like,
- did not understand the importance of piercing orientation,
 - did not thin orientation of the inhaler is important
 - children had difficulty pressing the button on the inhaler
- were confused by the instructions for use,
- experienced difficulties opening the blister pack, or
- gripping the capsules.

Novartis provided a root cause analysis on all use errors. In some cases, the reported use-related issues were determined to be associated with product design (i.e. piercing feedback is not noticeable, piercing force is high for some pediatric participants). However, in other cases, the root cause analysis only provides additional classification of use errors i.e. categorizing whether the error committed was a rule-based, knowledge-based, or memory failure. This type of analysis is not helpful in determining whether the test results, and particularly failures or patterns of subjective reports of difficulty with the use of the device were caused by either aspects of the design of the device, its labeling, the content or proximity of training, and whether product modifications are required.

Given the several study limitations i.e. use of empty capsules during testing, therefore, test participants would not get the feedback necessary during use and ensure that they successfully inhale a full dose, and insufficient number of study participants for at home and post 1-week assessment, this reviewer remains concerned that multiple subjects/subject pairs across all age range did not complete a successful dose. The reviewer is most concerned with the use errors preventing successful dosing were:

- Not orienting the inhaler mouthpiece correctly resulting in incomplete piercing, which may lead to inhalation of a capsule fragment
- Not removing and checking the capsule after inhalation
- Not inhaling twice from each capsule, or inhaling all 4 capsules
- Not depressing the button on the device with enough force to pierce the capsule
 - Pediatric users experienced difficulty to exert the required force to depress the button sufficiently

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

/s/

JOSEPH C DAVI

08/27/2012

This is a CDRH Human Factors review being checked in by the DAIP RPM on behalf of the CDRH reviewer.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: August 25, 2012

TO: J. Christopher Davi, Regulatory Project Manager
Shrimant Mishra, M.D., Medical Officer
Eileen Navarro-Almario, M.D., M.P.H., Clinical Team Leader
Division of Anti-Infective Products

FROM: Janice Pohlman, M.D., M.P.H.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Susan Thompson, M.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 201688

APPLICANT: Novartis Pharmaceuticals Corporation

DRUG: TOBI[®] Podhaler (tobramycin inhalation powder)
NME: No
THERAPEUTIC CLASSIFICATION: Standard review

INDICATIONS: Management of cystic fibrosis patients with *Pseudomonas aeruginosa*

CONSULTATION REQUEST DATE: February 28, 20112
INSPECTION SUMMARY GOAL DATE: August 19, 2012
DIVISION ACTION GOAL DATE: October 19, 2012
PDUFA DATE: October 19, 2012

I. BACKGROUND:

Cystic fibrosis (CF) is a genetic disorder characterized by a mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. The mutation causes an abnormality in chloride channels and chloride ion transport. The transport of other ions, such as sodium, is also affected. The faulty regulation of sodium absorption and inability to secrete chloride reduces the volume of liquid on airway surfaces leading to viscous endobronchial secretions. The thickened mucus is difficult to clear and becomes chronically colonized or infected by bacteria. Repeated infections cause damage to the respiratory tract. Respiratory disease is a major cause of morbidity and mortality in patients with CF. Pulmonary function tests (PFTs) are used to monitor a patient's disease progression, with the decrease in forced expiratory flow in one second (FEV₁) correlating with disease progression.

Tobramycin is an aminoglycoside antibacterial agent for treatment of bacterial infections in patients with CF. Tobramycin inhaled as a solution (TOBI®) delivered by nebulizer is approved for treatment of *Pseudomonas aeruginosa* infection in the United States and Europe. Tobramycin inhalation powder (TIP), the subject of this NDA, is designed for use in the same population as that for TOBI®, i.e. patients colonized with *P. aeruginosa*. TIP is formed of low density particles and is designed to be delivered with a T-326 dry powder inhaler (DPI) which is light, portable, and has no internal or external power source.

The Applicant submitted the results of three studies to support the approval of this application.

Study CTBM100C2301 (formerly TIP002 A01): “A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Phase 3 Trial to Assess the Efficacy and Safety of Tobramycin Inhalation Powder (TIP) in Cystic Fibrosis (CF) Subjects”

The study was a randomized, three-cycle, two-arm trial. The first cycle was double-blind, placebo controlled and subjects were randomized 1:1 to receive TIP or placebo. Upon completion of the first cycle, all subjects received TIP for two additional cycles. Each cycle consisted of 28 days on treatment followed by 28 days off treatment.

The primary objective of the study was to demonstrate the efficacy of a 28-day, twice daily (BID) dosing regimen of TIP versus placebo, as measured by the relative change in FEV₁ % predicted from baseline (Week 1/Cycle 1, Day 1) to the end of Cycle 1 dosing (Week 5/Cycle 1, Day 28).

One hundred and two patients (102) were randomized and 95/102 (93%) received study medication.

Study CTBM100C2302: “A randomized, open-label, multicenter, phase 3 trial to assess the safety of tobramycin inhalation powder compared to TOBI® in cystic fibrosis subjects”

The study was a randomized, open-label, active controlled, parallel-arm trial. Eligible patients were randomized to TIP or TOBI® in a 3:2 ratio. Treatment was administered for 28 days and was followed by 28 days off therapy (one cycle) for 3 cycles. The primary objective of the study was to evaluate the safety of twice daily (BID) dosing of TIP delivered with the T-326 inhaler, compared to TOBI® delivered with the PARI LC PLUS jet nebulizer and DeVilbiss PulmoAide compressor (or suitable alternative).

A total of 553 patients were randomized into the study; 517 received at least one unit of study medication and were included in the intent to treat and safety analysis populations. Approximately one third of patients were from the United States.

Study CTBM100C 2303: “A Randomized, Double-Blind, Placebo-Controlled, Multi-Center Phase 3 Study in Cystic Fibrosis (CF) Subjects to Assess Efficacy, Safety and Pharmacokinetics of Tobramycin Inhalation Powder from a Modified Manufacturing Process (TIP_{new})”

This was a double-blind, randomized, placebo-controlled study in subjects suffering from cystic fibrosis and no history of treatment with tobramycin (amended to none in the past 4 months), ages 6 to 21 years who were infected with *P. aeruginosa*. Patients were randomized in a 1:1 fashion to treatment with TIP_{new} or placebo for a period of 28 days. The study consisted of a 2 week screening phase, followed by the 28 day treatment cycle, followed by 28 days off therapy.

The primary objective of this study was to evaluate the efficacy of tobramycin inhalation powder after modifications in the manufacturing process (TIP_{new}) for treatment of infections with *P. aeruginosa* in cystic fibrosis subjects, assessed by relative change from baseline FEV₁ % predicted to Day 29, compared to placebo. The secondary objectives were to compare the safety profile and pharmacokinetics of TIP_{new} for the treatment of infections with *P. aeruginosa* in cystic fibrosis subjects compared to placebo

The study was terminated early due to enrollment difficulties. The Applicant claims that the placebo-controlled study design and requirement for TOBI naive patients with chronic *P. aeruginosa* infection limited enrollment to sites outside the United States. Sixty two of the planned 100 patients were enrolled; 32 patients in the TIP_{new} treatment group and 30 in the placebo treatment group. Fifty nine (95.2%) patients completed the study; the three patients who discontinued were in the TIP treatment group.

II. RESULTS (by Site):

Site # Name and Location of CI	Protocol # and # of Subjects	Inspection Date	Final Classification*
Site #501 Dr. Predrag Minic Mother and Child Health Institute 8 Radoja Dakica St. Belgrade Serbia 11070	CTBM100C2301 14 subjects	July 2 - 6, 2012	Pending (preliminary VAI)

Site # Name and Location of CI	Protocol # and # of Subjects	Inspection Date	Final Classification*
Site #701 Dr. Ivan Galabov Pediatric Clinic of Pulmonology, Nephrology and Neurology UMHAT "Sv.Marina" 1, Hristo Smimenski Str. 9010 Varna, Bulgaria	CTBM100C2301 10 subjects	May 7 - 11, 2012	Pending (preliminary VAI)
Site #702 Dr. Penka Perenovska 1 st Pediatric Clinic UMHAT "Alexandrovska" 1, "Georgi Sofiiski" Str. 1431 Sofia Bulgaria	CTBM100C2301 11 subjects	May 2 - 4, 2012	Pending (preliminary VAI)
Site #46 David E. Geller, M.D. The Nemours Children's Clinic – Orlando (NCC-O) 83 W. Columbia Street Orlando, FL 32806	CTBM100C2302 21 subjects	April 16 – 30, 2012	Pending (preliminary OAI)
Site #284 Dr. Ivanka Ognianova Galeva Clinic of Pediatrics UMHAT "Alexandrovska" 1 Georgi Sofiiski Str. 1431 Sofia Bulgaria	CTBM100C2303 8 subjects	May 14 - 18, 2012	Pending (preliminary VAI)

* Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and/or complete review of EIR is pending.

1. Dr. Predrag Minic
Mother and Child Health Institute
8 Radoja Dakica St.
Belgrade
Serbia 11070
 - a. What was inspected: For Study CTBM100C2301, at this site, 16 subjects were screened, 14 subjects were enrolled, and 13 subjects completed the study. Fourteen subjects' records were audited. The record audit included review of informed consent documentation, comparison of source documentation and case report forms to NDA line listings with particular attention paid to inclusion/exclusion criteria

compliance, primary efficacy endpoint data, identification of adverse events, and reporting of AEs in accordance with the protocol. There were no limitations to the inspection.

- b. General observations/commentary: Consistent with the routine clinical investigator compliance program assessments, during the inspection, data found in source documents and those measurements reported by the Applicant to the Agency in NDA 201688 were compared and verified. There was no under-reporting of adverse events with the exception of two non-serious events described below. The study was conducted under an IND at this site and the clinical investigator signed a Form FDA 1572. A Form FDA 483 was issued for:
 - i. The investigation was not conducted in accordance with the signed investigator statement and investigational plan. Specifically,
 - a. Protocol section 9.5.1.5.1 requires that serum pregnancy tests be performed for females of childbearing potential at screening (Visit 1) and follow-up/termination (Visit 11). Subject #501201, #501203, #501204, and #501209 had no documentation of such tests. Additionally there was no documentation that Subject #501201 had a urine pregnancy test performed at Visit 7 as required by protocol.
 - b. The protocol excluded subjects who received antipseudomonal antibiotics within 28 days prior to study drug administration. Subject #501205 began taking ciprofloxacin four days prior to the first dose of study medication.
 - c. Protocol section 9.5.4.2.1 lists procedures to be completed at baseline visit, Visit 2 (Cycle 1, day 1). These include pretreatment procedures, treatment with study drug, and post-treatment procedures. Subject #501207 had pre-treatment procedures performed five days before treatment and post-treatment procedures.
 - d. The following adverse events were not reported on CRFs: Subject #501208 had fever and headache noted at Visit 9 and Subject #501216 had varicella blisters and fever noted at Visit 2.

OSI Reviewer Comment: Although Subject #501201, #501203, #501204, and #501209 did not have serum pregnancy tests performed as required by protocol, the field investigator was able to find documentation indicating that these subjects had negative urine pregnancy tests at screening and Visits 7 and 9 (off study medication for 28 days). Although Subject #501201 did not have a urine pregnancy test at Visit 7, scheduled pregnancy tests before and after this timepoint were performed per protocol and were negative. Therefore, while this observation is consistent with a regulatory violation, there is no evidence that the safety of these subjects was compromised or that they experienced adverse events as a result of the CI's lack of compliance with protocol required procedures.

Prior treatment with ciprofloxacin in Subject #501205 and pretreatment procedures performed 5 days prior to treatment and post-treatment procedures in Subject #501207 had the potential to affect efficacy assessment, but these events were random and infrequent making it unlikely that they would significantly impact overall study results.

The adverse events not reported on the CRF were likely due to infection rather than drug since the event of “varicella and fever” in Subject #501208 was noted prior to treatment with study medication at Visit 2 and the event of “fever and headache” in Subject #501216 was noted at Visit 9 (following 28 days off study medication).

- ii. Permission by parents or guardians for the participation of children as subjects in a clinical investigation was not documented in accordance with and to the extent required by 21 CFR 50.27. Specifically, Subject #501208 (an 8 year old child) and a witness signed the consent form and assent form on 2/2/06. The subject began taking the study medication on 2/17/06. The parent/guardian did not sign the consent form until 2/7/07, after the subject had completed the study.

OSI Reviewer Comment: This is clearly a regulatory violation; however it does not impact data reliability for this study. The subject completed the study on August 9, 2006; adverse events noted for this subject over the course of the study included dysphonia, cough, pharyngitis, tooth ache, and elevated blood glucose. This issue was discussed with the Human Subject Protection Branch in the Division of Safety Compliance, and no additional regulatory action is recommended at this time.

- iii. Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation and informed consent. Specifically,
 - a. Records in the study file for Subject #501208 show the 4/17/06 Visit 7 FEV₁ values were .79 (9:28 AM) and .59 (10:05 AM) at pre- and post-dose timepoints, respectively. They were incorrectly reported on the CRF as .50 (8:20 AM) and .47 (9:15 AM), which were the FEV₁ values (and times) for Subject #501206 who had a visit the same day.
 - b. The medical file for Subject #501211 included at least three records indicating the subject was allergic to amikacin, an aminoglycoside. The study protocol excludes subjects with a known local or systemic hypersensitivity to aminoglycosides. There was no indication that the discrepancy was addressed until 6/22/06, after the subject was withdrawn from the study.
 - c. The original signed consent form for Subject #501205 is missing page 5 of 9.

OSI Reviewer Comment: These issues were sporadic in nature and are unlikely to have a significant impact on primary efficacy or safety analyses. Incorrect reporting of Visit 7 FEV₁ in Subject #501208 would not have had an impact on the primary efficacy endpoint which was measured as the change in FEV₁ % predicted at baseline (Visit 2) to the end of Cycle 1 of treatment (Visit 5). Enrollment of a patient with hypersensitivity to aminoglycosides was a violation of an exclusion criterion and could have presented a safety problem. However, preliminary review of the Establishment Inspection Report (EIR) indicates that Subject #501211 had received intravenous amikacin without untoward effects after the initial historical report of hypersensitivity to amikacin (hypersensitivity manifest as itching and redness). The subject was withdrawn from the study due to a pulmonary exacerbation of his CF.

- iv. The informed consent document lacked an explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights. Specifically, the consent forms signed by all study subjects or parents/guardians did not include the name and telephone number of the Local Ethics Committee and the Medicines and Medical Devices Agency of Serbia.

OSI Reviewer Comment: This is a regulatory violation, however it would not be expected to impact data reliability and there was no evidence identified during the inspection that the safety and welfare of enrolled subjects was adversely impacted. The CI, Dr. Minic, has not yet responded to Form FDA 483, Inspectional Observations.

- c. Assessment of data integrity:
Notwithstanding the discussion above regarding Subject #501205 (ciprofloxacin treatment initiated prior to randomization) and Subject #501207 (pretreatment assessment 5 days prior to treatment and post-treatment assessment), the data appear to be acceptable/reliable in support of the pending application. The review division may wish to consider the potential impact of issues related to these two subjects in their efficacy analysis.

Note: Observations noted above are based on the Form FDA 483 and preliminary review of the EIR; an inspection summary addendum will be generated if conclusions change upon final review of the EIR and discussion with the Office of Safety Compliance.

2. Dr. Ivan Galabov
Pediatric Clinic of Pulmonology, Nephrology and Neurology
UMHAT "Sv. Marina"
1, Hristo Smimenski Str.
9010 Varnia, Bulgaria

- a. What was inspected: For Study CTBM100C2301, at this site, 10 subjects were screened, 10 subjects were enrolled, and 10 subjects completed the study. The audit of 10 subjects' records included comparison of source documentation and CRFs to NDA line listings with particular attention paid to informed consent documentation, inclusion/exclusion criteria compliance, primary efficacy endpoint data, identification of adverse events, and reporting of AEs in accordance with the protocol. The FDA field investigator also reviewed logs of site monitoring visits and monitor correspondence, drug accountability records, and documentation of the IRB's approvals for the study and informed consent/assent forms. There were no limitations to the inspection.
- b. General observations/commentary: Consistent with the routine clinical investigator compliance program assessments, during the inspection, data found in source documents and those measurements reported by the Applicant to the Agency in NDA 201688 were compared and verified. There was no under-reporting of adverse events. The study was conducted under an IND at this site and the clinical investigator signed a Form FDA 1572. A Form FDA 483 Inspectional Observations was issued specifically for:
 - i. The investigation was not conducted in accordance with the signed investigator statement. Specifically, the investigator did not comply with the sponsor's request dated 9/20/06 to notify subjects to immediately stop taking their study medications. Study records indicate that Subject #701-210 continued to administer study drug up to and including a study visit to the clinic on 9/28/06 (Day 15 visit).

OSI Reviewer Comment: A memo in the subject's record from the Sponsor to the investigator dated September 20, 2006, stated that the clinical study was being placed on partial clinical hold because of safety concerns about increased levels of a degradation product in the placebo used in the study. In his response to Form FDA 483, Inspectional Observations, dated May 28, 2012, Dr. Galabov explained that the memo was sent as a fax and was not seen until Sept 25, 2006 when the office opened following a national holiday (September 22-24, 2006). The office was unable to reach the subject by telephone until Sept. 27, 2006 at which time the subject was told to discontinue the study medication. The study medication was administered at the site on September 28, 2006 by mistake. Delayed discontinuation only occurred with this one patient, and other subjects were discontinued in a more timely fashion.

The partial clinical hold was removed following a meeting of the Data Monitoring Committee (DMC) after an interim analysis detected no safety signal, and allowed the study to continue.

- ii. Failure to prepare or maintain adequate and accurate case histories with

respect to observations and data pertinent to the investigation.

Specifically,

- a. Subject #701-202's height was entered as 160 cm in an IVRS randomization record and spirometry reports, while height was recorded as 168 cm in the screening CRF.
- b. Subject #701-201's the dosing inhalation record for Visit 9 was inconsistent. The CRF states dosing start time of 10:45 which was changed via a data clarification form to 10:50. However progress notes indicate start time as 10:45, and the subject diary card records indicate start time as 10:30.
- c. Subject #701-207's case history was incomplete; original notes were not observed to document the subject's study clinic visit 6/6/06, although that was the date that the informed consent document was signed.

These were isolated observations, were not of a systemic nature, and do not impact data generated by this site.

In his response to Form FDA 483, Inspectional Observations, dated May 28, 2012, Dr. Galabov stated that the height of Subject #701-202 recorded in the screening CRF was an error. The height was correctly entered as 160 cm on the randomization form and spirometry reports where it was used to calculate FEV₁ % predicted. For Subject #701-201 above, the Visit 9 CRF originally stated that dosing time was 10:45. A data clarification form was sent to the site on October 3, 2006, and site personnel mistakenly made the change to 10:50. For Subject #701-207, the site thought they were following the formal requirements for informed consent, allowing a subject time to consider participation and questions. The formal screening procedures were performed at another visit.

- c. Assessment of data integrity:

Notwithstanding the observations noted above, the data provided by Dr. Galabov's site for Study CTBM100C2301 that were submitted to the Agency in support of NDA 201688 appear to be reliable and acceptable for use in support of the pending application.

Note: Observations noted above are based on the Form FDA 483 and preliminary review of the EIR; an inspection summary addendum will be generated if conclusions change upon final review of the EIR.

3. Dr. Penka Perenovska
1st Pediatric Clinic
UMHAT "Alexandrovska"
1, "Georgi Sofiiski" Str.
1431 Sofia, Bulgaria

- a. What was inspected: For Study CTBM100C2301, at this site, 13 subjects were screened, 11 subjects were enrolled, and 11 subjects completed the study. Eleven subjects' records were reviewed. The record audit included comparison of source documentation and CRFs to NDA line listings with particular attention paid to informed consent documentation, inclusion/exclusion criteria compliance, primary efficacy endpoint data, identification of adverse events, and reporting of AEs in accordance with the protocol. The FDA field investigator also reviewed the monitoring visit log, drug accountability records, documentation of the IRB's approval for the study, and the informed consent/assent forms used for the study. There were no limitations to the inspection.
- b. General observations/commentary: Consistent with the routine clinical investigator compliance program assessments, during the inspection, data found in source documents and those measurements reported by the Applicant to the Agency in NDA 201688 were compared and verified. There was no under-reporting of adverse events. A Form FDA 483, Inspectional Observations was issued to the clinical investigator for:

Failure to insure that the investigation was conducted in accordance with the investigational plan. Specifically:

- i. Pulmonary function tests were not always accurately recorded in study records. Specifically,
 - a. The screening FEV₁ value for Subject #702-203 (TIP) was entered as 1.12 L (51.03% predicted) on the randomization worksheet used for eligibility determination and study IVRS. However, the three associated spirometry reports indicated that the best test was 0.65 L (30.4% predicted).
 - b. For Subject #702-204 (placebo), the screening FEV₁ value was entered as 1.20 L on the randomization worksheet used for the study IVRS and eligibility determination. However, the three associated spirometry reports indicated the best FEV₁ was 1.23 L (80.1% predicted value).
 - c. The screening value for Subject #702-208 (placebo) was entered as 1.40 L on the randomization sheet and entered as 1.44 on the screening procedure CRF.
 - d. For Subject #702-209 (placebo), the Visit 2 pre-dose FEV₁ value was entered as 2.25 L on the Visit 2 worksheet dated 8/25/06. However, the maximum FEV₁ value reported in three available reports was 2.09 L.

OSI Reviewer Comment: The differences in FEV₁ noted above resulted in a variety of effects on randomization and primary efficacy determination. Subject #702-203 was randomized to an incorrect strata (≥ 50 - $\leq 80\%$ group) based on the FEV₁ recorded on the randomization worksheet rather than that based on

spirometry reports. Subject #702-204, should have been ineligible to enroll in the study with FEV₁ % predicted >80%. Subject #702-208 would have experienced no effect on eligibility or randomization. Since baseline FEV₁ % predicted is used for determining efficacy, recording an overestimate of FEV₁ % predicted for Subject #702-209 would make it harder to demonstrate that randomized study drug worked. While the number of errors is concerning, the errors themselves appear to each affect a different aspect of randomization or efficacy determination for each subject and would be unlikely to have a systematic effect on overall efficacy analyses. The findings were communicated to the clinical and statistical review team on August 20, 2012, and the reviewers concluded that the observed documentation errors would not result in a clear directional over/under estimation of FEV₁ % predicted change and that increasing the variability in estimates would lead to a more conservative analysis.

In her response to Form FDA 483, Inspectional Observations, dated May 22, 2012, Dr. Perenovska states that for Subject #702-203, the difference in reported FEV₁ was due to a transcription error which was identified and documented on a data clarification form. For Subject #702-204 and #702-208 the FEV₁ used for IVRS and eligibility determination reflected only 2 digits (in tenths instead of hundredths). Subject #702-209 FEV₁ was actually that of another patient. In her response, Dr. Perenovska outlined corrective measures to prevent these problems in the future.

- ii. IVRS procedures were not always followed for allocation of study test article.
 - a. Subject #702-204 was dispensed test article that had not been allocated through IVRS. A note to file indicated that the subject was allocated a test article based on its availability at the study site.
 - b. Subject #702-205 was dispensed test article that had not been allocated through the IVRS system. An IVRS notification dated 7/18/06 records that the subject was dispensed kit #2215 for Cycle #2 (unblinded). However the Cycle #2 dosing worksheet records two kits for the subject; kit #2215 from July 26 and kit # 1967 from July 11th. An IVRS notification was not observed for the kit #1967.
 - c. Records indicated that Subject #702-210 was dispensed and dosed with Cycle 2 test article (unblinded) on 10/30/06. The associated drug accountability form indicated that kit #2231 was used for one day only. There was no IVRS documentation for dispensing this kit to this subject. An IVRS dosing confirmation dated 10/30/06 indicated that kit #2234 was allocated from the system. An accountability form indicated that this kit was used for subsequent dosing of the subject.
 - d. Records indicated that Subject #702-211 was dispensed and dosed with Cycle 2 test article (unblinded) on 10/25/06. The associated study drug label indicates that kit #2233 was used. Notes indicate kit

was allocated outside of IVRS. An IVRS communication indicated that the IVRS subsequently allocated kit #2231 for subject's Cycle 2, although the kit was not used for this patient.

OSI Reviewer Comment: The primary efficacy endpoint was assessed prior to Cycle 2, so that the drug dispensing issues for Subject #702-205, #702-210, and #702-211 would not impact data reliability for assessment of the primary efficacy endpoint. It is not clear from the evidence presented whether the identified kits contained active study drug or placebo. Therefore, during the unblinded treatment cycle (Cycles 2), subjects may not have received active study therapy as called for by protocol. It is unlikely that the dispensing issues would have had much impact on safety assessment either, since patients continued on with a third cycle of open-label study treatment.

Based upon preliminary review of the establishment inspection report (EIR), the problem with Subject #702-204 was actually delayed start of centrally allocated drug which was considered to be a protocol deviation.

In her response to Form FDA 483, Inspectional Observations, dated May 22, 2012, Dr. Perenovska states that problems with the IVRS system initiated the events related to Subject #702-210 and #702-211. Her response outlines enhancing efforts to document problems as they arise.

c. Assessment of data integrity:

Notwithstanding the observations noted above, the data provided by Perenovska's site for Study CTBM100C2301 that were submitted to the Agency in support of NDA 201688 appear to be reliable and acceptable for use in support of the pending application. The review division may wish to consider performing a sensitivity analysis excluding Subject #702-204 and #702-209 based on the discussion noted above.

Note: Observations noted above are based on the Form FDA 483 and preliminary review of the EIR; an inspection summary addendum will be generated if conclusions change upon final review of the EIR.

4. David E. Geller, M.D.

The Nemours Children's Clinic – Orlando (NCC-O)
83 W. Columbia Street
Orlando, FL 32806

- a. What was inspected: For Study CTBM100C2302, at this site, 25 subjects were screened, 21 subjects were enrolled, and 18 subjects completed the study. Eleven subjects' records were reviewed during the inspection. The record audit included comparison of source documentation and CRFs to NDA line listings with particular

attention paid to informed consent documentation, inclusion/exclusion criteria compliance, primary efficacy endpoint data, identification of adverse events, and reporting of AEs in accordance with the protocol. Documentation of the IRB's approvals for the study and the informed consent/assent forms used for the study were also reviewed. There were no limitations to the inspection.

(b) (4)

- b. General observations/commentary: Consistent with the routine clinical investigator compliance program assessments, during the inspection, data found in source documents and those measurements reported by the Applicant to the Agency in NDA 201688 for Study CTBM100C2302 were compared and verified. The primary efficacy endpoint data was able to be verified. There was no under-reporting of adverse events. In general, the site followed Good Clinical Practices for this study.

Dr. Geller was not available during the inspection,

(b) (4)

- c. Assessment of data integrity:

(b) (4)

The data for Study CTBM100C2302 that were submitted to the Agency in support of NDA 201688 appear to be reliable and acceptable for use in support of the pending application.

Note: Observations noted above are based on the Form FDA 483 and preliminary review of the EIR; an inspection summary addendum will be generated if conclusions change upon final review of the EIR.

5. Dr. Ivanka Ognianova Galeva
Clinic of Pediatrics
UMHAT "Alexandrovska"
1 Georgi Sofiiski Str.
1431 Sofia, Bulgaria

- a. What was inspected: For Study CTBM100C2303, at this site, approximately 50 subjects were screened, eight subjects were enrolled, and eight subjects completed the study. Eight subjects' records were reviewed during the inspection. The record review included comparison of source documentation and CRFs to NDA line listings with particular attention paid to informed consent documentation, inclusion/exclusion criteria compliance, primary efficacy endpoint data, identification of adverse events, and reporting of AEs in accordance with the protocol. The FDA field investigator also reviewed the site monitoring log and feedback letters, drug accountability records, and documentation of IRB's approval for the study and informed consent/assent forms used in the study. There were no limitations to the inspection.
- b. General observations/commentary: Consistent with the routine clinical investigator compliance program assessments, during the inspection, data found in source documents and those measurements reported by the Applicant to the Agency in NDA 201688 were compared. There was no under-reporting of adverse events. This study was not conducted under IND; therefore, Dr. Galeva did not sign a Form FDA 1572 for this study. A Form FDA 483, Inspectional Observations, was issued to the CI for:
 - i. The investigation was not conducted in accordance with investigational plan, specifically:
 - a. A subject was enrolled and treated without first obtaining valid spirometry tests. Subject #008 (tobi) had screening spirometry (Visit 1) on 6/16/10 and a data clarification form dated 6/18/10 indicated that results were not acceptable for all efforts (five readings). The patient was randomized and had five pre-treatment and two post-treatment spirometry test efforts on 6/29/10. Data clarification forms indicate that results for both tests are not acceptable for all efforts.
 - b. Subjects were randomized into an incorrect treatment arm
 - i. Subject #004 (placebo) spirometry test data indicated screening % predicted FEV₁ was approximately 40%, but the subject was randomized into treatment group for FEV₁ % predicted \geq 50% and \leq 80%.
 - ii. Subject #005 (tobi) spirometry test data indicated screening % predicted FEV₁ was approximately 74%, but the subject was randomized into the treatment group for FEV₁ % predicted \geq 25% to $<$ 50%.
 - c. A subject was enrolled and randomized into the study although their FEV₁ % predicted was greater than 80%. The screening spirometry report for Subject #003 (tobi) indicated the subject had a % predicted FEV₁ of 80.2%.
 - ii. Failure to prepare or maintain adequate and accurate case histories with

respect to observations and data pertinent to the investigation, specifically:

- a. The screening pulmonary function report for Subject #002 (placebo) dated 11/20/09 indicated that the subject's FEV₁ % predicted was 107.81% which is greater than the upper limit for inclusion of 80%.
- b. There was no source documentation (i.e., pulmonary function report) to support the reported FEV₁% for Subject #002 for Visit 2 (baseline), visit date 12/7/09.
- c. For Subject #001 (placebo), an acceptable screening pulmonary function report (spirometry report) was not observed.
- d. Complete source records for spirometry tests were not maintained
 - i. Spirometry calibration logs were not maintained.
 - ii. While pulmonary function reports were printed and available, the underlying spirometry test data was archived in a format not readily available for review.

OSI Reviewer Comment: Four subjects enrolled in the trial either did not meet inclusion criteria for FEV₁ % predicted (Subjects #002 and #003) or had inadequate documentation of screening and /or baseline spirometry (Subjects #001 and #008). These findings were discussed with the clinical and statistical review teams on August 9 and 10, 2012. The statistical review team noted that subjects with screening FEV₁ % predicted values out of range (or missing) at screening all had baseline FEV₁ % predicted values within the target range; therefore, inclusion of their relative change measurements in the analyses would not be expected to have an effect on efficacy outcome. These protocol deviations were noted in review but sensitivity analyses excluding these patients were thought to be uninformative and were not performed.

Two Subjects (004 and 005) were randomized to incorrect strata. The impact of this finding was also discussed with the review team who advised that this finding would not significantly impact their determination of efficacy for the product. Review staff stated that randomization to the wrong stratum has no effect if the stratification factor was not predictive of response. In contrast, if the stratification factor was predictive of response, then randomization to the wrong stratum provides a conservative estimate of effect because the mis-randomization creates more heterogeneity within strata resulting in a less precise estimate of effect and a loss of statistical power.

Regarding spirometry calibration logs, the protocol does not include a statement requiring the maintenance of such a log. Instructions for use of the FlowScreen[®] CT (spirometer) for Trial CTBM100C2303 supplied by (b) (4) contain information on the Calibration Check Procedure. The instructions include the following statements, "You can document the results by pressing the <Print Screen> key. The printouts should be filed in the investigator files." In her response to Form FDA 483, Inspectional Observations, dated June 7, 2012, Dr. Galeva states

that there was no study requirement to maintain a calibration log. Spirometry device calibrations were performed prior to each subject visit according to the spirometry device manual. The spirometry device would not permit proceeding with subject tests before the calibration was done. Each printout of subject spirometry reports contain information for the date, time, and conditions of calibration performed.

c. Assessment of data integrity:

It is concerning that spirometry calibration logs are not available, especially given the issues noted with FEV₁ assessment at this site. However, the protocol does not require such a log, and the language in the instruction manual for the device is somewhat ambiguous stating you can document results (not you must/should document results) and the results should be filed in the investigator files. The FEV₁ issues described above were discussed with the review team who did not think a sensitivity analysis excluding subjects with out of range or missing FEV₁ would be informative. Notwithstanding the observations and issues noted above, the remaining data provided by Galeva's site for Study CTBM100C2303 that were submitted to the Agency in support of NDA 201688 appear to be reliable and acceptable for use in support of the pending application.

Note: Observations noted above are based on the Form FDA 483 and preliminary review of the EIR; an inspection summary addendum will be generated if conclusions change upon final review of the EIR.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

For Study CTBM100C2301, the preliminary classification of the clinical investigator inspections for Drs. Minic, Galabov, and Perenovska is Voluntary Action Indicated (VAI). Although regulatory violations were noted, based on preliminary review of the EIR and discussion with the clinical and statistical review teams, these were not considered to have a significant impact on data reliability. Based on the inspectional findings at these sites, efficacy and safety data obtained from this site can be considered reliable in support of the application. The review division may wish to consider performing sensitivity analyses excluding Subjects #501205 and #501207 at Dr. Minic's site, and Subjects #702-204 and #702-209 at Dr. Perenovska's site based on issues discussed previously.

For Study CTBM100C2302, the preliminary classification of Dr. Geller's site (b) (4)

[REDACTED]
[REDACTED] Based on the inspectional findings for Study CTBM100CC2302 at this site, efficacy and safety data obtained from this site may be considered reliable in support of the application.

For Study CTBM100C2303, the preliminary classification of Dr. Galeva's site is Voluntary Action Indicated (VAI). The regulatory violations regarding subjects who did not meet

eligibility criteria (FEV1 out of range or inadequate documentation of screening or baseline spirometry) were discussed with the review team. The review team determined that since subjects included in the analysis had baseline FEV1 % predicted within the targeted range, additional sensitivity analysis would be uninformative.

Note: Observations noted above are based on the Form FDA 483s and preliminary review of the EIRs; an inspection summary addendum will be generated if conclusions change upon final review of the EIRs.

{See appended electronic signature page}

Janice Pohlman, M.D., M.P.H.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan D. Thompson, M.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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

/s/

JANICE K POHLMAN
08/24/2012

SUSAN D THOMPSON
08/24/2012

Division of Anti-Infective Products

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: NDA 201,688

Name of Drug: TOBI Podhaler (tobramycin inhalation powder)

Applicant: Novartis Pharmaceutical Corporation

Labeling Reviewed

Submission Date: December 20, 2011

Receipt Date: December 21, 2011

Background and Summary Description: The Sponsor submitted a word version of their proposed package insert on December 21, 2011. The label was observed to be in Physician's Labeling Rule (PLR) format, as required by 21CFR 201.

Review

This reviewer performed a labeling review of the proposed label submitted by the Sponsor on December 20, 2011. The label was found to be substantially compliant with PLR requirements *from a general editorial and formatting perspective*. The label is acceptable for purposes of filing the application.

Recommendations

There are no recommendations for labeling changes at this time from Project Management. Any additional labeling changes/recommendations will be communicated to the Sponsor on or before September 21, 2012.

J. Christopher Davi, MS, Sr. Regulatory Project Manager	February 22, 2012
Regulatory Project Manager	Date
Maureen Dillon-Parker, Chief, Project Management Staff	February 22, 2012
Chief, Project Management Staff	Date

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

/s/

JOSEPH C DAVI
08/14/2012

MAUREEN P DILLON PARKER
08/14/2012

Division of Anti-Infective Products

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: NDA 201,688

Name of Drug: TOBI Podhaler (tobramycin inhalation powder)

Applicant: Novartis Pharmaceutical Corporation

Labeling Reviewed

Submission Date: December 20, 2011

Receipt Date: December 21, 2011

Background and Summary Description: The Sponsor submitted a word version of their proposed package insert on December 21, 2011. The label was observed to be in Physician's Labeling Rule (PLR) format, as required by 21CFR 201.

Review

This reviewer performed a labeling review of the proposed label submitted by the Sponsor on December 20, 2011. The label was found to be substantially compliant with PLR requirements *from a general editorial and formatting perspective*. The label is acceptable for purposes of filing the application.

Recommendations

There are no recommendations for labeling changes at this time from Project Management. Any additional labeling changes/recommendations will be communicated to the Sponsor on or before September 21, 2012.

J. Christopher Davi, MS, Sr. Regulatory Project Manager	February 22, 2012
Regulatory Project Manager	Date
Maureen Dillon-Parker, Chief, Project Management Staff	February 22, 2012
Chief, Project Management Staff	Date

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

/s/

JOSEPH C DAVI
02/22/2012

MAUREEN P DILLON PARKER
02/23/2012