

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**206756Orig1s000**

**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 # 206756	NDA Supplement #:S-	Efficacy Supplement Type SE-
Proprietary Name: Stiolto Respimat Inhalation Spray Established/Proper Name: tiotropium-olodaterol Dosage Form: Inhalation Spray Strengths: 2.5 mcg /2.5 mcg (respectively)		
Applicant: Boehringer Ingelheim Agent for Applicant (if applicable):		
Date of Application: May 22, 2014 Date of Receipt: May 22, 2014 Date clock started after UN:		
PDUFA Goal Date: May 22, 2015	Action Goal Date (if different):	
Filing Date: July 21, 2014	Date of Filing Meeting:	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 4 New combination		
Proposed indication(s)/Proposed change(s): COPD		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:  <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a></i>		
Type of BLA  <i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i>	<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)	
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 or pediatric rare disease priority review voucher was submitted, review classification is Priority.</i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority  <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>		
Resubmission after refuse to file? <input type="checkbox"/>		
Part 3 Combination Product? <input checked="" type="checkbox"/>  <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 checked="" type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input type="checkbox"/> Rolling Review <input 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):				
List referenced IND Number(s): IND 76397				
<b>Goal Dates/Product Names/Classification Properties</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
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>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
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>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
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 New Application and New Supplement Notification Checklists for a list of all classifications/properties at: <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</a></i>  <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Application Integrity Policy</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:	<input type="checkbox"/>	<input type="checkbox"/>		
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		UF ID# PD3011479

<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 checked="" type="checkbox"/> Paid  <input 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><b>505(b)(2)</b>  <b>(NDAs/NDA Efficacy Supplements only)</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></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><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></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><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></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 505(b)(2) review staff in the Immediate Office of New Drugs</i></p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>																	
<p>Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</p> <p><i>Check the Electronic Orange Book at:</i>  <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a></p> <p><b>If yes, please list below:</b></p> <table border="1" data-bbox="203 1482 1349 1619"> <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><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></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 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>																				
<p><b>Exclusivity</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug</i></p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>																		

<b>Designations and Approvals list at:</b> <a href="http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</a>				
<b>If another product has orphan exclusivity</b> , 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>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ( <i>NDAs/NDA efficacy supplements only</i> )  If yes, # years requested: not specified (“under provisions of 21 CFR 314.108”)  <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use ( <i>NDAs only</i> )?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<b>If yes</b> , 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 the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>For BLAs:</b> Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act?  <i>If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM</i>  <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

<b>Format and Content</b>	
<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 checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)
<b>If mixed (paper/electronic) submission</b> , which parts of the	



<p>Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?</p> <p><i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p>Is form FDA 3674 included with authorized signature?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i></p> <p><i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> 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 FD&amp;C Act 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>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b>For paper submissions only:</b> 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>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<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>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b><u>PREA</u></b></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)<sup>2</sup></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 &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<p><b>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</b></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<p><b>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?</b></p> <p><i>If no, request in 74-day letter</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<p><b>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)?</b></p> <p><i>If no, request in 74-day letter</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<p><b><u>BPCA</u> (NDAs/NDA efficacy supplements only):</b></p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i></p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<b>Proprietary Name</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p>Is a proposed proprietary name submitted?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>REMS</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a REMS submitted?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

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

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

<i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>				
<b>Prescription Labeling</b>	<input type="checkbox"/> <b>Not applicable</b>			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input checked="" type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL format?  <i>If no, request applicant to submit SPL before the filing date.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		Division agreed
Is the PI submitted in PLR format? <sup>4</sup>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , 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>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>OTC Labeling</b>	<input checked="" type="checkbox"/> <b>Not Applicable</b>			
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)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted?	<input type="checkbox"/>	<input type="checkbox"/>		

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

<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Other Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>If yes, specify consult(s) and date(s) sent:</i>				
<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of Phase 2 meeting(s)? <b>Date(s):</b> CMC - 7/29/2011 Meeting preliminary Responses Minutes – 8/4/2011	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> Written Responses 9/9/2013	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** 7/10/2014

**NDA:** 206756

**PROPRIETARY NAME:** Stiolto Respimat

**ESTABLISHED/PROPER NAME:** tiotropium/olodaterol

**DOSAGE FORM/STRENGTH:** Inhalation Spray

**APPLICANT:** Boehringer Ingelheim

**PROPOSED INDICATION(S):** Chronic obstructive pulmonary disease (COPD)

**BACKGROUND:**

**REVIEW TEAM:**

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Christine Chung	Y
	CPMS/TL:	Sandy Barnes	N
Cross-Discipline Team Leader (CDTL)	Anthony Durmowicz		Y
Clinical	Reviewer:	Robert Lim	Y
	TL:	Anthony Durmowicz	Y
Social Scientist Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		
OTC Labeling Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		
Clinical Microbiology ( <i>for antimicrobial products</i> )	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Dinko Rekić	Y
	TL:	Satjit Brar	Y
Biostatistics	Reviewer:	Lan Zeng	Y
	TL:	Ruthanna Davi	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Andrew Goodwin	N
	TL:	Timothy Robison	N
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) ( <i>for BLAs/BLA efficacy supplements</i> )	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Eugenia Nashed	Y
	TL:	Craig Bertha Eric Duffy	N Y
Quality Microbiology ( <i>for sterile products</i> )	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Lissa Owens	
	TL:		
OSE/DRISK (REMS)	Reviewer:	Felicia Duffy	
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	Anthony Orenca	Y
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers			
Other attendees	Ritesh Jain Timothy McGovern, Marcie Wood Sara Stradley Nichelle Rashid Margie Goulding Kathleen Donohue Yu (Jade) Wang		

**FILING MEETING DISCUSSION:**

<p><b>GENERAL</b></p> <ul style="list-style-type: none"> <li>• 505(b)(2) filing issues: <ul style="list-style-type: none"> <li>○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</li> <li>○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature?</li> </ul> </li> </ul> <p>Describe the scientific bridge (e.g., BA/BE studies):</p>	<input checked="" type="checkbox"/> Not Applicable  <input type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Electronic Submission comments</li> </ul> <p><b>List comments:</b></p>	<input type="checkbox"/> Not Applicable
<p><b>CLINICAL</b></p> <p><b>Comments:</b></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"> <li>Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no</b>, explain: No high enrolling sites, mono-products already approved or will be approved</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p> <p><i>If no, for an NME NDA or original BLA , include the reason. For example:</i></p> <ul style="list-style-type: none"> <li><i>this drug/biologic is not the first in its class</i></li> <li><i>the clinical study design was acceptable</i></li> <li><i>the application did not raise significant safety or efficacy issues</i></li> <li><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></li> </ul>	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined  Reason: <i>this drug/biologic is not the first in its class</i>
<ul style="list-style-type: none"> <li>Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>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?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b></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"> <li>Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p><b>BIostatistics</b></p>	<input type="checkbox"/> Not Applicable

<p><b>Comments:</b></p>	<input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p> <p><b>Comments:</b></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
<p><b>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>PRODUCT QUALITY (CMC)</b></p> <p><b>Comments:</b></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
<p><b><u>Environmental Assessment</u></b></p> <ul style="list-style-type: none"> <li>• Categorical exclusion for environmental assessment (EA) requested?   <b>If no</b>, was a complete EA submitted?   <b>If EA submitted</b>, consulted to EA officer (OPS)?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Quality Microbiology (for sterile products)</u></b></p> <ul style="list-style-type: none"> <li>• Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable  <input type="checkbox"/> YES <input type="checkbox"/> NO

<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection?</li> <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ?</li> </ul> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b><u>CMC Labeling Review</u></b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Review issues for 74-day letter
<p><b>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</b></p> <ul style="list-style-type: none"> <li>• Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application?</li> <li>• If so, were the late submission components all submitted within 30 days?</li> </ul>	<input checked="" type="checkbox"/> N/A <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• What late submission components, if any, arrived after 30 days?</li> </ul>	
<ul style="list-style-type: none"> <li>• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>REGULATORY PROJECT MANAGEMENT</b>	
<p><b>Signatory Authority:</b> Badrul Chowdhury, Division Director</p> <p><b>Date of Mid-Cycle Meeting</b> (for NME NDAs/BLAs in “the Program” PDUFA V): 11/6/2014</p> <p><b>21<sup>st</sup> Century Review Milestones (see attached)</b> (listing review milestones in this document is optional):</p> <p><b>Comments:</b></p>	
<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing.  <u>Review Issues:</u>  <input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter.  <input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):  <u>Review Classification:</u>  <input checked="" type="checkbox"/> Standard Review  <input type="checkbox"/> Priority Review
<b>ACTIONS ITEMS</b>	
<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"/>	<p>If priority review:</p> <ul style="list-style-type: none"> <li>• 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)</li> <li>• notify OMPQ (so facility inspections can be scheduled earlier)</li> </ul>
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
<input type="checkbox"/>	<p>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 in the CST eRoom at:  <a href="http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f">http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f</a> ]</p>
<input type="checkbox"/>	Other

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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CHRISTINE H CHUNG  
05/22/2015

**DEPARTMENT OF HEALTH & HUMAN SERVICES**

**Public Health Service**

**Food and Drug Administration**

Center for Devices and Radiological Health

Office of Compliance, Division of Manufacturing & Quality

Respiratory, ENT, General Hospital, Ophthalmic Devices Branch

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**DATE:** May 20, 2015

**TO:** Eugenia Nashed, WO 21-2510 CDER/ONDQA

eugenia.nashed@fda.hhs.gov

Craig Bertha, WO21-2548 OMPT/CDER/OPS/ONDQA/DNDQAIH

Craig.Bertha@fda.hhs.gov

Office of combination products at [combination@fda.gov](mailto:combination@fda.gov)

**RPM:** Youbang Liu

**Through:** Francisco Vicenty, Chief, REGO, DMQ, OC, CDRH, OMPT. WO-66,  
Room 2642 Rakhi Dalal for Francisco Vicenty

**Rakhi M.  
Panguluri -S**

Digitally signed by Rakhi M. Panguluri -S  
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,  
ou=People,  
0.9.2342.19200300.100.1.1=1300200210,  
cn=Rakhi M. Panguluri -S  
Date: 2015.05.20 11:01:20 -04'00'

**From:** Viky Verna, REGO, DMQ, OC, CDRH, OMPT. WO-66, Room 2628

**Applicant:** Boehringer Ingelheim Pharmaceuticals, Inc.

900 Ridgebury Road, PO Box 368

Ridgefield, Connecticut 06877

**Application #** NDA 206756 - ICC1400405

**Product Name:** STIOLTO – Respimat Inhalation Spray

**Consult** Please evaluate relevant facilities named in the application for

**Instructions:** their device-constituent responsibilities and determined if a  
device inspection is required.

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The Office of Compliance at CDRH received a consult request from CDER to evaluate the applicant's compliance with applicable Quality System Requirements for the

approvability of the combination product STIOLTO – Respimat Inhalation Spray, NDA 206756.

### **PRODUCT DESCRIPTION**

The Stiolto Respimat combination product is indicated as a once daily maintenance bronchodilator treatment of chronic obstructive pulmonary disease (COPD). It consists of a sterile, aqueous, multi-dose solution of tiotropium bromide monohydrate, a long-acting muscarinic antagonist (LAMA) and olodaterol hydrochloride, a long-acting 2-adrenoceptor agonist (LABA), for oral inhalation delivered by the Respimat inhaler.

One carton of the combination product contains two entities, the cartridge with the inhalation solution and the RESPIMAT inhaler. Prior to first use, the patient inserts the cartridge into the inhaler. After reaching the labeled number of actuations, the RESPIMAT inhaler is blocked from further use by a locking mechanism. Both RESPIMAT and the inserted cartridge are then disposed of.



tiotropium+olodaterol RESPIMAT (b) (4) inhaler

The RESPIMAT inhaler (manufactured by Boehringer Ingelheim microParts GmbH) is a hand held, pocket sized oral inhalation device that uses mechanical energy to generate a slow moving aerosol cloud of medication (“soft mist”). It meters a small volume of the inhalation solution (b) (4)

### **DESK REVIEW**

The application was searched for documents pertaining to applicable 21 CFR part 820 regulations for this combination product.

### **Management Control, CFR 820.20**

The firm provided a table which lists the firms involved in the manufacturing of the combination product with their responsibilities. However, the list did not contain a list of the manufactures involved in the manufacturing of the device components of the combination product. Also, the sponsor did not provide an organizational structure diagram which displays how it controls all firms involved in the manufacturing of the combination product to ensure that it is designed and produced in accordance with the applicable quality system requirements. The sponsor firm did not summarize how it will ensure that its quality policy is understood, implemented, and maintained at all levels of the organization.

The information provided by the firm has inadequately addressed the requirements of 21 CFR 820.20.

#### RESPONSE REVIEW

The firm's response dated November 26, 2014, is adequate. Boehringer Ingelheim Pharma GmbH & Co. KG (BIPKG) confirmed that it has ultimate management responsibility and oversight for Stiolto RESPIMAT Inhalation Spray; including the release and associated quality review of this final packaged combination product. The sponsor described how the firms responsible for each constituent part comply with the governing requirement to satisfy 21 CFR Part 4. The firm also provided an organization structure diagram which depicts how the manufacturing at Respimat Device Dortmund (responsible for RESPIMAT Inhaler production), and the manufacturing Respimat Drug Product Ingelheim, (responsible for production of the "RESPIMAT cartridge" and the finished combination product) are both managed by the same manufacturing department. Analogously, the quality units at BIPKG and BlmP are part of a single overarching quality department.

#### **Design Control, General, CFR 820.30**

The sponsor described several tests performed to control the design of the combination product. Specifically, the firm provided the results of the risk analysis, suitability testing, stability tests, compatibility studies with primary packaging components, and extractables and leachables studies performed.

However, the sponsor did not provide information on its Design Control system with the plan used to control the design of the combination product and its evolution in accordance to 21 CFR 820.30.

The information provided by the firm has inadequately addressed the requirements of 21 CFR 820.30.

#### RESPONSE REVIEW

The firm's response dated November 26, 2014, is adequate. Boehringer Ingelheim confirmed it has a Design Control Procedure in place which defines the requirements and responsibilities

for the Design Control System within Boehringer Ingelheim Pharma GmbH & Co. KG (BIPKG) and Boehringer Ingelheim microParts (BlmP). The procedure ensures that medical devices are designed and developed in accordance with applicable regulatory requirements (e.g., 21 CFR 820.30, ISO 13485, Directive 93/42/EEC) covering the entire life cycle of the combination product. The sponsor also summarized how the Design Control System was applied to the Stiolto combination product, addressing both the device constituent part and the intended use of the combination product, including the needs of the user and patient. It was used to ensure that the device constituent part is appropriate for use with the drug (e.g. compatibility, in-use stability, cleaning and handling studies, etc.). The development of the (b) (4) RESPIMAT inhaler is documented in a Design History File (DHF).

**Production and Process Controls, 820.70**

The firm provided a description on how the manufacturing of the combination product is performed and controlled. The manufacturing process consists of (b) (4)

[Redacted]

Production Flow

The firm provided a production flow diagram.

(b) (4)

[Redacted]

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.70.

#### **Purchasing Controls, 820.50**

The firm provided a list of firms involved in the manufacturing of the combination product. Also, it stated that the RESPIMAT inhaler is manufactured by Boehringer Ingelheim microParts GmbH. However, the sponsor did not provide information on its purchasing controls system which specifies controls applicable to its suppliers. The firm did not explain how it will balance supplier assessments and receiving acceptance activities to ensure that products from suppliers will continue to meet set specifications. Furthermore, the sponsor did not explain how it will ensure that changes made by contractors/suppliers will not affect the final combination product.

The information provided by the firm has inadequately addressed the requirements of 21 CFR 820.50.

#### **RESPONSE REVIEW**

The firm's response dated November 26, 2014, is adequate. Per the response, procedures are established at Boehringer Ingelheim (BI), which define BI's purchasing control system (BI's supplier management system). As part of this purchasing control system, procedures for the selection, qualification/approval and continuous evaluation/control of suppliers are in place. The firm described the steps and processes involved in the selection, qualification/approval and continuous evaluation/control of suppliers. Purchasing specifications and supplier agreements ensure effective control over delivered materials and contracted services by requiring suppliers to notify Boehringer Ingelheim of intended changes.

#### **Receiving Acceptance Activities, 820.80(b)**

The sponsor provided a list of firms involved in the manufacturing of the combination product. Also, it stated that the RESPIMAT inhaler is manufactured by another firm, Boehringer Ingelheim microParts GmbH. However, the sponsor did not provide information on how it will ensure products received from suppliers meet set specifications through receiving acceptance activities. Information on defined acceptance/rejection criteria and on the disposition of rejected or nonconforming products, was not provided.

The information provided by the firm has inadequately addressed the requirements of 21 CFR 820.80(b).

#### **RESPONSE REVIEW**

The firm's response dated November 26, 2014, is adequate. The sponsor clarified that the manufacturer of the RESPIMAT device constituent part of the combination drug product is not a supplier, but is a BI manufacturing site, i.e., Boehringer Ingelheim microParts (BI mP) in

Dortmund Germany. Boehringer Ingelheim Pharma GmbH & Co. KG (BIPKG), the manufacturer of the combination drug product, receives lots of RESPIMAT inhalers that have undergone testing and release by BImP according to the device specifications. Given the unified organizational structure of BI, the Device lots released by BImP are used in BIPKG manufacturing of the combination drug product with no further receiving testing of the device constituent part. However, BIPKG performs final release testing for the final combination product (i.e., Cartridge + Inhaler) which includes parameters related to inhalation performance.

#### **Final Acceptance Activities, 820.80(d)**

The sponsor described the final release activities on the final assembled combination product which takes into consideration both the cartridge and the inhaler to ensure specifications are met. The analytical release of each marketed tiotropium+olodaterol RESPIMAT inhalation spray drug product batch is based on the combination of test parameters related to the cartridge batch containing the inhalation solution and on test parameters related to the inhaler performance. The specifications (test parameters, acceptance criteria and analytical procedures) were provided.

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.80(d).

#### **Corrective and Preventive Action (CAPA), 820.100**

The sponsor did not provide any information on its Corrective and Preventive Action (CAPA) System.

The information provided by the firm has inadequately addressed the requirements of 21 CFR 820.100.

#### **RESPONSE REVIEW**

The firm's response dated November 26, 2014, is adequate. Boehringer Ingelheim (BI) confirmed that it has written procedures established for CAPA management. CAPAs are used to correct non-conformities, defects or other undesirable situations to prevent recurrence (corrective action) and to prevent occurrence (preventive action). The BI CAPA system aids in the identification and implementation of product and process improvements, and increases product and process understanding. The sponsor described its CAPA system which covers the different input sources, root cause investigation, change requests, and effectiveness checks.

#### **Desk Review Recommendation**

This application was deficient overall. Additional information is required for an adequate desk review.

#### **REGULATORY HISTORY**

After reviewing the application, the following facilities were identified as being subject to applicable Medical Device Regulations under 21 CFR part 820:

1. Boehringer Ingelheim Pharma GmbH & Co. KG (Ingelheim)  
Binger Straße 173  
Ingelheim am Rhein, 55216 Germany  
FEI: 3002806556

Responsibility: Manufacturing, packaging, labeling, release and stability testing.

An Inspection of the firm was performed on 02/24/2014 to 03/07/2014 which was classified as VAI. The systems covered include the Quality System, Production System, and the Laboratory Control System. Profile classes covered were TCM (Tablets, Prompt Release), CHG (Capsules, Prompt Release), CSN (Non-Sterile API by Chemical Synthesis), SLQ (Sterile Liquid) and TTR (Tablets, Extended Release).

The previous inspection of the firm was conducted on 11/5-12/12 and was classified OAI. The inspection was a pre-approval for NDA 203108 Olodaterol Respimat Inhalation Spray, and a routine cGMP inspection.

#### UPDATED

A pre-approval inspection was performed at the firm for the Stiolto - NDA 206756 application on January 19-23, 2015. The inspection was classified as NAI.

#### **RECOMMENDATION**

The firm's response dated November 26, 2014, is adequate and addressed the deficiencies previously noted.

The recommended pre-inspection of Boehringer Ingelheim Pharma GmbH & Co. KG (Ingelheim) was conducted and deemed acceptable.

Therefore, the Office of Compliance at CDRH recommends approval of application NDA 206756 for the Stiolto combination product.

**Viky  
Verna -A**

Digitally signed by Viky Verna -A  
DN: c=US, o=U.S. Government,  
ou=HHS, ou=FDA, ou=People,  
cn=Viky Verna -A,  
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623  
Date: 2015.05.20 10:07:12 -04'00'

LT Viky Verna, MS BME, MS Pharm

Prepared: VVerna: 10/1/14

Reviewed: FMLast name: Month/Day/Year

NDA 206756 - ICC1400405

## **INSPECTIONAL GUIDANCE**

Firm to be inspected:

1. Boehringer Ingelheim Pharma GmbH & Co. KG (Ingelheim)  
Binger Straße 173  
Ingelheim am Rhein, 55216 Germany

FEI: 3002806556

CDRH recommends the inspection under the applicable Medical Device Regulations of Boehringer Ingelheim Pharma GmbH & Co. KG (Ingelheim) located at Binger Straße 173, Ingelheim am Rhein, 55216 Germany (FEI: 3002806556).

A comprehensive baseline Level 2 inspection is recommended focusing on Management Responsibility (21 CFR 820.20), Purchasing Controls (21 CFR 820.50), CAPA (21 CFR 820.100), Final Acceptance Activities (21 CFR 820.80), and Design Controls (21 CFR 820.30) for the STIOLTO – Respimat Inhalation Spray (NDA 206756 - ICC1400405).

Additionally, evaluate the manufacturing activities associated with the manufacturing/assembly of the finished combination product, including in process and final acceptance activities.

## **POST-INSPECTION FOLLOW-UP**

The establishment inspection report (EIR) for the firm should be shared with CDRH (The EIR should be assigned to CDER and then sent to CDRH as a consult for review). If the inspection is being classified Official Action Indicated (OAI), the District should consider recommending appropriate regulatory action with consultation from CDER and CDRH and whether the violation is drug or device related.

Questions regarding this consult should be referred to one of the following individuals:

### **Primary Contact**

Viky Verna  
Biomedical Engineer,  
REGO  
DMQ  
Office of Compliance, WO66 RM 2628  
Phone: 301-796-2909

### **Secondary Contacts (if Primary is unavailable and a timely answer is required)**

Francico Vicenty  
Chief  
REGO  
DMQ  
Office of Compliance, WO66 RM 2642  
Phone: 301-796- 5770

**THIS ATTACHMENT IS NOT TO BE PROVIDED TO THE FIRM OR SHOWN TO THEM  
DURING THE INSPECTION. THIS ATTACHMENT CONTAINS PREDECISIONAL  
INFORMATION**

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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EUGENIA M NASHED  
05/21/2015

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

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

**Memorandum**

**Date:** February 18, 2015

**To:** Christine Ford, R.Ph.  
Regulatory Project Manager  
Division of Pulmonary, Allergy, and Rheumatology Products  
(DPARP)

**From:** Matthew Falter, Pharm.D.  
Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)

**CC:** Kathleen Klemm, Pharm.D.  
Group Leader, OPDP

**Subject:** OPDP Labeling Consult Response  
NDA # 206756  
STIOLTO™ RESPIMAT® (tiotropium bromide and olodaterol)  
Inhalation Spray

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In response to DPARP's, September 8, 2014, consult request, OPDP has reviewed the proposed Prescribing Information (PI), Medication Guide (MG), Instructions for Use (IFU), and Carton/Container labeling for STIOLTO™ RESPIMAT® (tiotropium bromide and olodaterol) Inhalation Spray (Stiolto).

OPDP has reviewed the proposed PI. Our comments on the proposed PI are based on the proposed draft-marked up labeling titled "206756 scpi 2-6-15.doc", which was sent via e-mail from DPARP to OPDP on February 9, 2015. OPDP comments on the proposed PI are provided directly in the marked-up document attached (see below).

OPDP has reviewed the proposed Carton and Container Labeling submitted by the applicant and available in the EDR at:

- <\\cdsesub1\evsprod\nda206756\0000\m1\us\ct6025a.pdf>
- <\\cdsesub1\evsprod\nda206756\0000\m1\us\l6026a.pdf>
- <\\cdsesub1\evsprod\nda206756\0000\m1\us\l6027a.pdf>
- <\\cdsesub1\evsprod\nda206756\0000\m1\us\l6028a.pdf>
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- <\\cdsesub1\evsprod\nda206756\0000\m1\us\l6048a.pdf>
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- <\\cdsesub1\evsprod\nda206756\0000\m1\us\l6051a.pdf>
- <\\cdsesub1\evsprod\nda206756\0000\m1\us\l6052a.pdf>

OPDP does not have any comments on the proposed Carton and Container labels at this time.

OPDP's review and comments on the proposed MG and proposed IFU was conducted jointly with the Division of Medical Policy Programs (DMPP). This review was provided under separate cover and submitted into DARRTS on February 17, 2015.

Thank you for the opportunity to comment on the proposed labeling. If you have any questions regarding this review, please contact me at [matthew.falter@fda.hhs.gov](mailto:matthew.falter@fda.hhs.gov) or at 6-2287.

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

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/s/  
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MATTHEW J FALTER  
02/18/2015

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

**PATIENT LABELING REVIEW**

Date: February 17, 2015

To: Badrul Chowdhury, MD  
Director  
**Division of Pulmonary, Allergy, and Rheumatology  
Products (DPARP)**

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

From: Sharon W. Williams MSN, BSN, RN  
Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**  
Matthew J. Falter, Pharm.D., R.Ph.  
Regulatory Review Officer  
**Office of Prescription Drug Promotion (OPDP)**

Subject: Review of Patient Labeling: Medication Guide (MG) and  
Instructions for Use (IFU)

Drug Name (established name): STIOLTO RESPIMAT (tiotropium bromide and olodaterol)

Dosage Form and Route: Inhalation spray, for oral inhalation use

Application Type/Number: NDA 206756

Applicant: Boehringer Ingelheim Pharmaceuticals, Inc.

## 1 INTRODUCTION

On May 23, 2014, Boehringer Ingelheim submitted for the Agency's review an Original New Drug Application for STIOLTO RESPIMAT (tiotropium bromide and olodaterol) inhalation spray. STIOLTO RESPIMAT (tiotropium bromide and olodaterol) inhalation spray is indicated for the long-term once-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to requests by the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) on September 8, 2014, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for STIOLTO RESPIMAT (tiotropium bromide and olodaterol) inhalation spray.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and DMEPA deferred to DMPP to provide IFU review comments.

## 2 MATERIAL REVIEWED

- Draft STIOLTO RESPIMAT (tiotropium bromide and olodaterol) MG and IFU received on May 23, 2014, and received by DMPP and OPDP on February 9, 2015.
- Draft STIOLTO RESPIMAT (tiotropium bromide and olodaterol) Prescribing Information (PI) received on May 23, 2014, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 9, 2015.
- Approved STRIVERDI RESPIMAT comparator labeling dated July 31, 2014.

## 3 REVIEW METHODS

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 MG and IFU document using the Arial font, size 11.

In our collaborative review of the MG and IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU are consistent with the Prescribing Information (PI)
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG and IFU are consistent with the approved comparator labeling where applicable.

#### **4 CONCLUSIONS**

The MG and IFU are acceptable with our recommended changes.

#### **5 RECOMMENDATIONS**

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG and IFU are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

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

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/s/  
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SHARON W WILLIAMS  
02/17/2015

MATTHEW J FALTER  
02/17/2015

MELISSA I HULETT  
02/17/2015

LASHAWN M GRIFFITHS  
02/17/2015

**REGULATORY PROJECT MANAGER  
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW  
OF THE PRESCRIBING INFORMATION**

**Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements**

**Application:** NDA 206756

**Application Type:** New NDA

**Name of Drug:** Stiolto (tiotropium/olodaterol) Respimat Inhalation Spray

**Applicant:** Boehringer-Ingelheim

**Receipt Date:** May 22, 2014

**Goal Date:** May 22, 2015

**1. Regulatory History and Applicant's Main Proposals**

Boehringer-Ingelheim submitted a New Drug Application for tiotropium/olodaterol for long term, once daily bronchodilator treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema. The PI includes a Medication Guide and Patient Instructions for Use.

The submission also contains carton and container labeling.

**2. Review of the Prescribing Information**

This review is based on the applicant's submitted Word format of the prescribing information (PI) dated May 23, 2014. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

**3. Conclusions/Recommendations**

No SRPI format deficiencies identified in the review of this PI need to be forwarded to the applicant.

# Selected Requirements of Prescribing Information

## Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

## Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

### HIGHLIGHTS GENERAL FORMAT

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

**Comment:**

- YES** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. **Instructions to complete this item:** If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

**Comment:**

- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

**Comment:**

- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

**Comment:**

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

**Comment:**

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

**Comment:**

- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required

## Selected Requirements of Prescribing Information

• <b>Initial U.S. Approval</b>	Required
• <b>Boxed Warning</b>	Required if a BOXED WARNING is in the FPI
• <b>Recent Major Changes</b>	Required for only certain changes to PI*
• <b>Indications and Usage</b>	Required
• <b>Dosage and Administration</b>	Required
• <b>Dosage Forms and Strengths</b>	Required
• <b>Contraindications</b>	Required (if no contraindications must state “None.”)
• <b>Warnings and Precautions</b>	Not required by regulation, but should be present
• <b>Adverse Reactions</b>	Required
• <b>Drug Interactions</b>	Optional
• <b>Use in Specific Populations</b>	Optional
• <b>Patient Counseling Information Statement</b>	Required
• <b>Revision Date</b>	Required

\* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

**Comment:**

### HIGHLIGHTS DETAILS

#### Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

**Comment:**

#### Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: “**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**” The name of drug product should appear in UPPER CASE letters.

**Comment:**

#### Product Title in Highlights

- YES** 10. Product title must be **bolded**.

**Comment:**

#### Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

**Comment:**

#### Boxed Warning (BW) in Highlights

- YES** 12. All text in the BW must be **bolded**.

**Comment:**

- YES** 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and

## Selected Requirements of Prescribing Information

other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

**Comment:**

- YES** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.

**Comment:**

- YES** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).

**Comment:**

### Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

**Comment:**

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

**Comment:**

- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

**Comment:**

### Indications and Usage in Highlights

- YES** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

**Comment:**

### Dosage Forms and Strengths in Highlights

- N/A** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

**Comment:**

## Selected Requirements of Prescribing Information

### Contraindications in Highlights

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

### Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

### Patient Counseling Information Statement in Highlights

- YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

Comment:

### Revision Date in Highlights

- YES** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment:

## Selected Requirements of Prescribing Information

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### Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.  
*Comment:*
- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.  
*Comment:*
- YES** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.  
*Comment:*
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.  
*Comment:*
- YES** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].  
*Comment:*
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.  
*Comment:*
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “\*Sections or subsections omitted from the full prescribing information are not listed.”  
*Comment:*

## Selected Requirements of Prescribing Information

### Full Prescribing Information (FPI)

#### FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

<b>BOXED WARNING</b>
<b>1 INDICATIONS AND USAGE</b>
<b>2 DOSAGE AND ADMINISTRATION</b>
<b>3 DOSAGE FORMS AND STRENGTHS</b>
<b>4 CONTRAINDICATIONS</b>
<b>5 WARNINGS AND PRECAUTIONS</b>
<b>6 ADVERSE REACTIONS</b>
<b>7 DRUG INTERACTIONS</b>
<b>8 USE IN SPECIFIC POPULATIONS</b>
<b>8.1 Pregnancy</b>
<b>8.2 Labor and Delivery</b>
<b>8.3 Nursing Mothers</b>
<b>8.4 Pediatric Use</b>
<b>8.5 Geriatric Use</b>
<b>9 DRUG ABUSE AND DEPENDENCE</b>
<b>9.1 Controlled Substance</b>
<b>9.2 Abuse</b>
<b>9.3 Dependence</b>
<b>10 OVERDOSAGE</b>
<b>11 DESCRIPTION</b>
<b>12 CLINICAL PHARMACOLOGY</b>
<b>12.1 Mechanism of Action</b>
<b>12.2 Pharmacodynamics</b>
<b>12.3 Pharmacokinetics</b>
<b>12.4 Microbiology (by guidance)</b>
<b>12.5 Pharmacogenomics (by guidance)</b>
<b>13 NONCLINICAL TOXICOLOGY</b>
<b>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</b>
<b>13.2 Animal Toxicology and/or Pharmacology</b>
<b>14 CLINICAL STUDIES</b>
<b>15 REFERENCES</b>
<b>16 HOW SUPPLIED/STORAGE AND HANDLING</b>
<b>17 PATIENT COUNSELING INFORMATION</b>

**Comment:**

- YES** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

**Comment:**

## Selected Requirements of Prescribing Information

- N/A** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

### FULL PRESCRIBING INFORMATION DETAILS

#### FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

Comment:

#### BOXED WARNING Section in the FPI

- YES** 36. In the BW, all text should be **bolded**.

Comment:

- YES** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

Comment:

#### CONTRAINDICATIONS Section in the FPI

- N/A** 38. If no Contraindications are known, this section must state “None.”

Comment:

#### ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

- N/A** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

Comment:

#### PATIENT COUNSELING INFORMATION Section in the FPI

- YES** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

## Selected Requirements of Prescribing Information

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

**Comment:**

- YES** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

**Comment:**

# Selected Requirements of Prescribing Information

## Appendix A: Format of the Highlights and Table of Contents

### HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]  
Initial U.S. Approval: [year]

**WARNING: [SUBJECT OF WARNING]**

*See full prescribing information for complete boxed warning.*

- [text]
- [text]

### RECENT MAJOR CHANGES

[section (X.X)] [m/year]  
[section (X.X)] [m/year]

### INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

### DOSAGE AND ADMINISTRATION

- [text]
- [text]

### DOSAGE FORMS AND STRENGTHS

[text]

### CONTRAINDICATIONS

- [text]
- [text]

### WARNINGS AND PRECAUTIONS

- [text]
- [text]

### ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### DRUG INTERACTIONS

- [text]
- [text]

### USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

### FULL PRESCRIBING INFORMATION: CONTENTS\*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 [text]

2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 [text]

5.2 [text]

6 ADVERSE REACTIONS

6.1 [text]

6.2 [text]

7 DRUG INTERACTIONS

7.1 [text]

7.2 [text]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Labor and Delivery

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 [text]

14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

\*Sections or subsections omitted from the full prescribing information are not listed.

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/s/  
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CHRISTINE H CHUNG  
01/26/2015

SANDRA L BARNES  
01/27/2015

**DEPARTMENT OF HEALTH & HUMAN SERVICES**

**Public Health Service**

**Food and Drug Administration**

Center for Devices and Radiological Health

Office of Compliance, Division of Manufacturing & Quality

Respiratory, ENT, General Hospital, Ophthalmic Devices Branch

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**DATE:** October 1, 2014

**TO:** Eugenia Nashed, WO 21-2510 CDER/ONDQA  
eugenia.nashed@fda.hhs.gov

Craig Bertha, WO21-2548 OMPT/CDER/OPS/ONDQA/DNDQAIH

Craig.Bertha@fda.hhs.gov

Office of combination products at [combination@fda.gov](mailto:combination@fda.gov)

**RPM:** Youbang Liu

**Through:** Francisco Vicenty, Chief, REGO, DMQ, OC, CDRH, OMPT. WO-66,  
Room 2642

**Francisco Vicenty -S**

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**From:** Viky Verna, REGO, DMQ, OC, CDRH, OMPT. WO-66, Room 2628

**Applicant:** Boehringer Ingelheim Pharmaceuticals, Inc.  
900 Ridgebury Road, PO Box 368  
Ridgefield, Connecticut 06877

**Application #** NDA 206756 - ICC1400405

**Product Name:** STIOLTO – Respimat Inhalation Spray

**Consult Instructions:** Please evaluate relevant facilities named in the application for their device-constituent responsibilities and determined if a device inspection is required.

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The Office of Compliance at CDRH received a consult request from CDER to evaluate the applicant's compliance with applicable Quality System Requirements for the

approvability of the combination product STIOLTO – Respimat Inhalation Spray, NDA 206756.

### **PRODUCT DESCRIPTION**

The Stiolto Respimat combination product is indicated as a once daily maintenance bronchodilator treatment of chronic obstructive pulmonary disease (COPD). It consists of a sterile, aqueous, multi-dose solution of tiotropium bromide monohydrate, a long-acting muscarinic antagonist (LAMA) and olodaterol hydrochloride, a long-acting 2-adrenoceptor agonist (LABA), for oral inhalation delivered by the Respimat inhaler.

One carton of the combination product contains two entities, the cartridge with the inhalation solution and the RESPIMAT inhaler. Prior to first use, the patient inserts the cartridge into the inhaler. After reaching the labeled number of actuations, the RESPIMAT inhaler is blocked from further use by a locking mechanism. Both RESPIMAT and the inserted cartridge are then disposed of.



tiotropium+olodaterol RESPIMAT<sup>(b) (4)</sup> inhaler

The RESPIMAT inhaler (manufactured by Boehringer Ingelheim microParts GmbH) is a hand held, pocket sized oral inhalation device that uses mechanical energy to generate a slow moving aerosol cloud of medication (“soft mist”). It meters a small volume of the inhalation solution <sup>(b) (4)</sup>

### **DESK REVIEW**

The application was searched for documents pertaining to applicable 21 CFR part 820 regulations for this combination product.

### **Management Control, CFR 820.20**

The firm provided a table which lists the firms involved in the manufacturing of the combination product with their responsibilities. However, the list did not contain a list of the manufactures involved in the manufacturing of the device components of the combination product. Also, the sponsor did not provide an organizational structure diagram which displays how it controls all firms involved in the manufacturing of the combination product to ensure that it is designed and produced in accordance with the applicable quality system requirements. The sponsor firm did not summarize how it will ensure that its quality policy is understood, implemented, and maintained at all levels of the organization.

The information provided by the firm has inadequately addressed the requirements of 21 CFR 820.20.

**Design Control, General, CFR 820.30**

The sponsor described several tests performed to control the design of the combination product. Specifically, the firm provided the results of the risk analysis, suitability testing, stability tests, compatibility studies with primary packaging components, and extractables and leachables studies performed.

However, the sponsor did not provide information on its Design Control system with the plan used to control the design of the combination product and its evolution in accordance to 21 CFR 820.30.

The information provided by the firm has inadequately addressed the requirements of 21 CFR 820.30.

**Production and Process Controls, 820.70**

The firm provided a description on how the manufacturing of the combination product is performed and controlled. The manufacturing process consists of (b) (4)

[REDACTED]

Production Flow

The firm provided a production flow diagram.

(b) (4)



The information provided by the firm has adequately addressed the requirements of 21 CFR 820.70.

### **Purchasing Controls, 820.50**

The firm provided a list of firms involved in the manufacturing of the combination product. Also, it stated that the RESPIMAT inhaler is manufactured by Boehringer Ingelheim microParts GmbH. However, the sponsor did not provide information on its purchasing controls system which specifies controls applicable to its suppliers. The firm did not explain how it will balance supplier assessments and receiving acceptance activities to ensure that products from suppliers will continue to meet set specifications. Furthermore, the sponsor did not explain how it will ensure that changes made by contractors/suppliers will not affect the final combination product.

The information provided by the firm has inadequately addressed the requirements of 21 CFR 820.50.

### **Receiving Acceptance Activities, 820.80(b)**

The sponsor provided a list of firms involved in the manufacturing of the combination product. Also, it stated that the RESPIMAT inhaler is manufactured by another firm, Boehringer Ingelheim microParts GmbH. However, the sponsor did not provide information on how it will ensure products received from suppliers meet set specifications through receiving acceptance activities. Information on defined acceptance/rejection criteria and on the disposition of rejected or nonconforming products, was not provided.

The information provided by the firm has inadequately addressed the requirements of 21 CFR 820.80(b).

### **Final Acceptance Activities, 820.80(d)**

The sponsor described the final release activities on the final assembled combination product which takes into consideration both the cartridge and the inhaler to ensure specifications are met. The analytical release of each marketed tiotropium+olodaterol RESPIMAT inhalation spray drug product batch is based on the combination of test parameters related to the cartridge batch containing the inhalation solution and on test parameters related to the inhaler performance. The specifications (test parameters, acceptance criteria and analytical procedures) were provided.

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.80(d).

### **Corrective and Preventive Action (CAPA), 820.100**

The sponsor did not provide any information on its Corrective and Preventive Action (CAPA) System.

The information provided by the firm has inadequately addressed the requirements of 21 CFR 820.100.

### **Desk Review Recommendation**

This application was deficient overall. Additional information is required for an adequate desk review.

### **REGULATORY HISTORY**

After reviewing the application, the following facilities were identified as being subject to applicable Medical Device Regulations under 21 CFR part 820:

1. Boehringer Ingelheim Pharma GmbH & Co. KG (Ingelheim)  
Binger Straße 173  
Ingelheim am Rhein, 55216 Germany

FEI: 3002806556

Responsibility: Manufacturing, packaging, labeling, release and stability testing (including micro testing).

An Inspection of the firm was performed on 02/24/2014 to 03/07/2014 which was classified as VAI. The systems covered include the Quality System, Production System, and the Laboratory Control System. Profile classes covered were TCM (Tablets, Prompt Release), CHG (Capsules, Prompt Release), CSN (Non-Sterile API by Chemical Synthesis), SLQ (Sterile Liquid) and TTR (Tablets, Extended Release).

The previous inspection of the firm was conducted on 11/5-12/12 and was classified OAI. The inspection was a pre-approval for NDA 203108 Olodaterol Respimat Inhalation Spray, and a routine cGMP inspection.

### **Deficiencies to be conveyed to the applicant**

The following deficiencies have been identified while doing the desk review of application NDA 206756, in reference to applicable 21 CFR 820 regulations for the manufacturing of the finished combination product:

1. The information provided by your firm has inadequately addressed the requirements of 21 CFR 820.20. Your firm provided a table which lists the firms involved in the manufacturing of the combination product with their

responsibilities. However, your firm did not provide an organizational structure diagram which displays how it controls all firms involved in the manufacturing of the combination product to ensure that the product is designed and produced in accordance with the applicable quality system requirements. The firm with the ultimate responsibility over final packaged combination product release and the associated Device History File was not specified.

2. Your firm described several tests performed to validate the design of the combination product. However, your firm did not provide information on its Design Control system with the plan used to control the design of the combination product and its evolution in accordance to 21 CFR 820.30. Your firm did not provide any information covering the Design Input, Design output and Design Validation/Verification, including design changes, for the overall finished combination product in order to ensure that specified design requirements are met.
3. The information provided by your firm has inadequately addressed the requirements of 21 CFR 820.50. Your firm provided a list of firms involved in the manufacturing of the combination product, including the manufacturer of the RESPIMAT inhaler. However, your firm did not provide information a purchasing control system which specifies controls applicable to your suppliers. Your firm did not explain how it will balance supplier assessments and receiving acceptance activities to ensure that products from suppliers will continue to meet set specifications. Furthermore, your firm did not explain how it will ensure that changes made by contractors/suppliers will not affect the final combination product.
4. The information provided by your firm has inadequately addressed the requirements of 21 CFR 820.80(b). Your firm did not provide information on how it will ensure products received from suppliers meet set specifications through receiving acceptance activities. Information on defined acceptance/rejection criteria and on the disposition of rejected or nonconforming products, was not provided.
5. The information provided by your firm has inadequately addressed the requirements of 21 CFR 820.100. Your firm did not provide any information on its Corrective and Preventive Action (CAPA) System.

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

### **RECOMMENDATION**

The Office of Compliance at CDRH has completed the evaluation of application NDA 206756 and has the following recommendations:

Application NDA 206756 approvability under the Medical Device Regulations should be delayed until the sponsor provided the additional information requested and an adequate desk review of the application has been completed.

Application NDA 206756 approvability under the Medical Device Regulations should be delayed until the inspection of Site one Boehringer Ingelheim Pharma GmbH & Co. KG (Ingelheim) have been conducted and the site is deemed acceptable.

**Viky  
Verna -S**

Digitally signed by Viky Verna -S  
DN: c=US, o=U.S. Government,  
ou=HHS, ou=FDA, ou=People,  
cn=Viky Verna -S,  
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LT Viky Verna, MS BME, MS Pharm

Prepared: VVerna: 10/1/14

Reviewed: FMLast name: Month/Day/Year

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NDA 206756 - ICC1400405

## **INSPECTIONAL GUIDANCE**

Firm to be inspected:

1. Boehringer Ingelheim Pharma GmbH & Co. KG (Ingelheim)  
Binger Straße 173  
Ingelheim am Rhein, 55216 Germany

FEI: 3002806556

CDRH recommends the inspection under the applicable Medical Device Regulations of Boehringer Ingelheim Pharma GmbH & Co. KG (Ingelheim) located at Binger Straße 173, Ingelheim am Rhein, 55216 Germany (FEI: 3002806556).

A comprehensive baseline Level 2 inspection is recommended focusing on Management Responsibility (21 CFR 820.20), Purchasing Controls (21 CFR 820.50), CAPA (21 CFR 820.100), Final Acceptance Activities (21 CFR 820.80), and Design Controls (21 CFR 820.30) for the STIOLTO – Respimat Inhalation Spray (NDA 206756 - ICC1400405).

Additionally, evaluate the manufacturing activities associated with the manufacturing/assembly of the finished combination product, including in process and final acceptance activities.

## **POST-INSPECTION FOLLOW-UP**

The establishment inspection report (EIR) for the firm should be shared with CDRH (The EIR should be assigned to CDER and then sent to CDRH as a consult for review). If the inspection is being classified Official Action Indicated (OAI), the District should consider recommending appropriate regulatory action with consultation from CDER and CDRH and whether the violation is drug or device related.

Questions regarding this consult should be referred to one of the following individuals:

### **Primary Contact**

Viky Verna  
Biomedical Engineer,  
REGO  
DMQ  
Office of Compliance, WO66 RM 2628  
Phone: 301-796-2909

### **Secondary Contacts (if Primary is unavailable and a timely answer is required)**

Francico Vicenty  
Chief  
REGO  
DMQ  
Office of Compliance, WO66 RM 2642  
Phone: 301-796- 5770

**THIS ATTACHMENT IS NOT TO BE PROVIDED TO THE FIRM OR SHOWN TO THEM  
DURING THE INSPECTION. THIS ATTACHMENT CONTAINS PREDECISIONAL  
INFORMATION**

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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YOUBANG LIU  
10/29/2014

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## **LABEL AND LABELING REVIEW**

Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

**\*\*\* This document contains proprietary information that cannot be released to the public\*\*\***

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**Date of This Review:** September 2, 2014

**Requesting Office or Division:** Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

**Application Type and Number:** NDA 206756

**Product Name and Strength:** Stiolto Respimat (Tiotropium Bromide and Olodaterol)  
Inhalation Spray 2.5 mcg/2.5 mg per actuation

**Product Type:** Multi-Ingredient Product

**Rx or OTC:** Rx

**Applicant/Sponsor Name:** Boehringer Ingelheim

**Submission Date:** May 22, 2014

**OSE RCM #:** 2014-1149

**DMEPA Primary Reviewer:** Lissa C. Owens, PharmD

**DMEPA Team Leader:** Kendra Worthy, PharmD

**DMEPA Associate Director:** Lubna Merchant, M.S., PharmD

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## 1 REASON FOR REVIEW

This review evaluates the proposed container labels, carton labeling, prescribing information, and instructions for use for Stiolto Respimat (Tiotropium Bromide and Olodaterol) Inhalation Spray for risk of medication error in response to a request from the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP). DPARP requested this as part of their evaluation for new NDA 206756.

## 2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

<b>Table 1. Materials Considered for this Label and Labeling Review</b>	
<b>Material Reviewed</b>	<b>Appendix Section (for Methods and Results)</b>
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B
Previous DMEPA Reviews	N/A
Human Factors Study	N/A
ISMP Newsletters	N/A
Other	N/A
Labels and Labeling	G

N/A=not applicable for this review

## 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Tiotropium Bromide and Olodaterol are currently marketed as single ingredient products, but not as a combination product. In addition, the Respimat device is currently marketed with other products (Combivent Respimat and Striverdi Respimat). We did not retrieve any errors related to label and labeling with the currently marketed Respimat device.

We performed a risk assessment of the proposed container labels, carton and insert labeling, and instructions for use to identify deficiencies that may lead to medication errors. Additionally, we also compared the label and labeling of Stiolto Respimat to Combivent Respimat and Striverdi Respimat to ensure that they are well differentiated from each other.

DMEPA finds the proposed container labels, carton and insert labeling, and instructions for use acceptable.

#### **4 CONCLUSION**

DMEPA concludes that the proposed container labels, carton and insert labeling, and instructions for use are acceptable at this time. We defer to the Division of Medical Policy Programs (DMPP) for further comments and/or recommendations.

## APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

### APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Stiolto Respimat that Boehringer Ingelheim submitted on May 22, 2014.

<b>Table 2. Relevant Product Information for Stiolto Respimat</b>	
<b>Initial Approval Date</b>	N/A
<b>Active Ingredient</b>	Tiotropium Bromide and Olodaterol
<b>Indication</b>	Maintenance treatment of bronchospasm associated with chronic obstructive pulmonary diseases (COPD) and for reducing COPD exacerbations
<b>Route of Administration</b>	Oral inhalation
<b>Dosage Form</b>	Inhalation Spray
<b>Strength</b>	2.5 mcg/2.5 mcg per actuation
<b>Dose and Frequency</b>	2 inhalations once daily
<b>How Supplied</b>	Carton containing one Stiolto Respimat cartridge and one Stiolto Respimat inhaler
<b>Storage</b>	25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F)

## APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

### B.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on August 15, 2014 using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter.<sup>2</sup>

<b>Table 3: FAERS Search Strategy</b>	
<b>Date Range</b>	<b>April 18, 2014 – August 15, 2014 (limited to the date of our last search in OSE RCM 2014-753)</b>
<b>Product</b>	<b>Combivent Respimat</b>
<b>Event (MedDRA Terms)</b>	<b>Medication Errors [HLGT] Product Packaging Issues [HLT] Product Label Issues [HLT] Product Quality Issues (NEC)[HLT]</b>

### B.2 Results

Our search did not retrieve any cases.

### B.4 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>.

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<sup>2</sup> The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>.

## **APPENDIX G. LABELS AND LABELING**

### **G.1 List of Labels and Labeling Reviewed**

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>1</sup> along with postmarket medication error data, we reviewed the following Stiolto Respimat labels and labeling submitted by Boehringer Ingelheim on May 22, 2014.

- Container label
- Carton labeling
- Professional Sample label
- Professional Sample Carton Labeling
- Institution labels
- Institution Carton Labeling
- Instructions for Use

### **G.2 Label and Labeling Images**



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

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

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/s/  
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LISSA C OWENS  
09/02/2014

KENDRA C WORTHY  
09/02/2014

LUBNA A MERCHANT  
09/03/2014