

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206756Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 206756

SUPPL # N/A

HFD # 570

Trade Name

Stiolto Respimat

Generic Name

tiotropium/olodaterol

Applicant Name

Boehringer-Ingelheim

Approval Date, If Known

May 21, 2015

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

Did not specify, "pursuant to 21 CFR 314.50(j)"

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 21395 1/30/2004 tiotropium Handihaler

NDA# 203108 7/31/2014 olodaterol Respimat

NDA# 021936 9/24/2014 tiotropium Respimat

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical

investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently

demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Trial 1237.5 and Trial 1237.6

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

1237.5

1237.6

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
!
IND # 76397 YES ! NO
! Explain:

Investigation #2 !
!
IND # 76397 YES ! NO
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1
!
! YES ! NO
! Explain: ! Explain:

Investigation #2
!
! YES ! NO
! Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

=====
Name of person completing form:
Christine Ford, RPh
Title: Sr. Regulatory Management Officer
Thru: Ladan Jafari, CPMS
Date: May 20, 2015

Name of Office/Division Director signing form:
Badrul A. Chowdhury, MD, PhD
Title: Director, Division of Pulmonary, Allergy, and Rheumatology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

CHRISTINE H CHUNG
05/21/2015

BADRUL A CHOWDHURY
05/21/2015

Pediatric Research Equity Act (PREA) Waiver Request, Deferral Request/Pediatric Plan and Assessment Template(s)

BACKGROUND	
Please check all that apply: <input checked="" type="checkbox"/> Full Waiver <input type="checkbox"/> Partial Waiver <input type="checkbox"/> Pediatric Assessment <input type="checkbox"/> Deferral/Pediatric Plan	
BLA/NDA#: 206756	
PRODUCT PROPRIETARY NAME: Stiolto Respimat	ESTABLISHED/GENERIC NAME: tiotropium-olodaterol
APPLICANT/SPONSOR: Boehringer-Ingelheim	
PREVIOUSLY APPROVED INDICATION/S:	
(1) <u>None</u>	
(2) _____	
(3) _____	
(4) _____	
PROPOSED INDICATION/S:	
(1) <u>COPD</u>	
(2) _____	
(3) _____	
(4) _____	
BLA/NDA STAMP DATE: 05/22/14	
PDUFA GOAL DATE: 05/22/15	
SUPPLEMENT TYPE: N/A	
SUPPLEMENT NUMBER: N/A	

Reference ID: 3707718

Reference ID: 3773847

Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

NEW active ingredient(s) (includes new combination); indication(s); dosage form; dosing regimen; or route of administration?

Has the sponsor submitted a Proposed Pediatric Study Request (PPSR) or does the Division believe there is an additional public health benefit to issuing a Written Request for this product, even if the plan is to grant a waiver for this indication? (Please note, Written Requests may include approved and unapproved indications and may apply to the entire moiety, not just this product.)

Yes *No*

Is this application in response to a PREA (Postmarketing Requirement) PMR? Yes *No*

If Yes, PMR # _____ NDA # _____

Does the division agree that this is a complete response to the PMR? Yes *No*

If Yes, to either question Please complete the Pediatric Assessment Template.

If No, complete all appropriate portions of the template, including the assessment template if the division believes this application constitutes an assessment for any particular age group.

Reference ID: 3707718

Reference ID: 3773847

WAIVER REQUEST

Please attach:

- Draft Labeling (If Waiving for Safety and/or Efficacy) from the sponsor unless the Division plans to change. If changing the sponsor's proposed language, include the appropriate language under Question 4 in this form.
- Pediatric Record – in darrrts

1. Pediatric age group(s) to be waived. 0-18 years
2. Reason(s) for waiving pediatric assessment requirements (*Choose one. If there are different reasons for different age groups or indications, please choose the appropriate reason for each age group or indication. This section should reflect the Division's thinking.*)

- Studies are impossible or highly impractical (e.g. the number of pediatric patients is so small or is geographically dispersed). (Please note that in the DARRTS record, this reason is captured as "Not Feasible.") If applicable, chose from adult-related conditions on the next page
- The product would be ineffective and/or unsafe in one or more of the pediatric group(s) for which a waiver is being requested. Note: If this is the reason the studies are being waived, this information **MUST** be included in the pediatric use section of labeling. Please provide the draft language you intend to include in the label. The language must be included in section 8.4 and describe the safety or efficacy concerns in detail.
- The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients **and** is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested.
- Reasonable attempts to produce a pediatric formulation for one or more of the pediatric age group(s) for which the waiver is being requested have failed. (Provide documentation from Sponsor) Note: Sponsor must provide data to support this claim for review by the Division, and this data will be publicly posted. (*This reason is for Partial Waivers Only*)

3. Provide justification for Waiver:

COPD does not exist in the pediatric population

4. Provide language Review Division is proposing for Section 8.4 of the label if different from sponsor's proposed language:

Adult-Related Conditions that do not occur in pediatrics and qualify for a waiver

These conditions qualify for waiver because studies would be impossible or highly impractical

Age-related macular degeneration	Cancer:
Alzheimer's disease	Basal cell
Amyotrophic lateral sclerosis	Bladder
Atherosclerotic cardiovascular disease	Breast
Benign Prostatic Hyperplasia	Cervical
Chronic Obstructive Pulmonary Disease	Colorectal
Erectile Dysfunction	Endometrial
Infertility	Gastric
Menopausal and perimenopausal disorders	Hairy cell leukemia
Organic amnesic syndrome	Lung (small & non-small cell)
(not caused by alcohol or other psychoactive substances)	Multiple myeloma
Osteoarthritis	Oropharynx (squamous cell)
Parkinson's disease	Ovarian (non-germ cell)
Postmenopausal Osteoporosis	Pancreatic
Vascular dementia/ Vascular cognitive disorder/impairment	Prostate
Actinic Keratosis	Renal cell
	Uterine

DEFERRAL REQUEST

Please attach:

Pediatric Record

1. Age groups included in the deferral request:
2. Where deferral is only requested for certain age groups, reason(s) for not including entire pediatric population in deferral request:
3. Reason/s for requesting deferral of pediatric studies in pediatric patients with disease: *(Choose one. If there are different reasons for different age groups or indications, please choose the appropriate reason for each age group or indication. This section should reflect the Division's thinking.)*
 - a. Adult studies are completed and ready for approval
 - b. Additional safety or effectiveness data needed (describe)
 - c. Other (specify)
4. Provide projected date for the submission of the pediatric assessment (deferral date):
5. Did applicant provide certification of grounds for deferring assessments? Yes No
6. Did applicant provide evidence that studies will be done with due diligence and at the earliest possible time? Yes No

SPONSOR'S PROPOSED PEDIATRIC PLAN

1. Has a pediatric plan been submitted to the Agency? Yes No
2. Does the division agree with the sponsor's plan? Yes No
3. Did the sponsor submit a timeline for the completion of studies (must include at least dates for protocol submission, study completion and studies submitted)? Yes No

- a. Protocol Submission:
- b. Study Completion:
- c. Study Submission:

4. Has a Written Request been issued? Yes No (If yes and the WR matches the proposed pediatric plan, please attach a copy. It is not necessary to complete the remainder of this document)
5. Has a PPSR been submitted? Yes No (If yes, you may submit a draft WR and have PeRC review WR and deferral/plan at the same time.)

Please note that the remainder of this section should be completed based on what the Division is requiring regardless of what the sponsor is proposing.

DIVISION'S PROPOSED PK, SAFETY, AND EFFICACY TRIAL

Please complete as much of the information below as possible. Please note that the portions of the document that are shaded are not required for early stage pediatric plans but are useful if available.

Types of Studies/Study Design:

Nonclinical Studies:

Clinical Studies:

Age group and population (indication) in which study will be performed:

This section should list the age group and population exactly as it is in the plan.

Example:

Study 1: patients aged X to Y years.

Study 2: sufficient number of subjects to adequately characterize the pharmacokinetics in the above age groups.

Number of patients to be studied or power of study to be achieved:

Example:

Study 1: X subjects in each treatment arm and be powered to show that (drug name, concentration, form etc) DRUG is not inferior to the active comparator. 50% must be females and 25% must be less than 3 years.

Study 2: This study is powered and structured to detect a 30% change in (drug name, concentration, form etc) DRUG clearance and other relevant pharmacokinetic parameters.

Entry criteria:

This section should list pertinent inclusion/exclusion criteria.

Example:

*Entry criteria: Pediatric patients with disease x diagnosed with laboratory test of LFTs
Patients must have a negative pregnancy test if female.*

Clinical endpoints:

Example:

Study 1: Clinical outcome and safety will be the primary endpoints.

Study 2: The primary pharmacokinetic analysis of (drug name, concentration, form etc) DRUG should attempt to include all the patients in the study with determination of the following parameters: single dose and steady state AUC, C_{max}, T_{max}, and CL/F.

Timing of assessments:

Example: baseline, week 1, 4, and 6

<p>Statistical information (statistical analyses of the data to be performed): <i>Example:</i> <i>Study 1 non-inferiority: two-sided 95% confidence interval (CI) of treatment difference in improvement rates should be within 25% of the control's response rate.</i> <i>Study 2: descriptive statistical methods for AUC, C_{max}, T_{max}, C_{1/2} and compared to adults.</i></p>
<p>Division comments on product safety: Are there any safety concerns currently being assessed? <input type="checkbox"/> Yes <input type="checkbox"/> No Are there safety concerns that require us to review post-marketing safety data before fully designing the pediatric studies? <input type="checkbox"/> Yes <input type="checkbox"/> No Will a DSMB be required? <input type="checkbox"/> Yes <input type="checkbox"/> No Other comments:</p>
<p>Division comments on product efficacy:</p>
<p>Division comments on sponsor proposal to satisfy PREA:</p>

Reference ID: 3707718

Reference ID: 3773847

PeRC ASSESSMENT TEMPLATE

Please attach:

- Proposed Labeling from the sponsor unless the Division plans to change. If changing the language, include the appropriate language at the end of this form.*
- Pediatric Record*

Date of PREA PMR:

Description of PREA PMR: *(Description from the PMC database is acceptable)*

Was Plan Reviewed by PeRC? Yes No If yes, did sponsor follow plan?

If studies were submitted in response to the Written Request (WR), provide the annotated WR in lieu of completing the remainder of the Pediatric Assessment template.

Indication(s) that were studied:

This section should list the indication(s) exactly as written in the *protocols*.

Example:

DRUG for the treatment of the signs and symptoms of disease x.

Number of Centers _____

Number and Names of Countries _____

Drug information:

Examples in italics

- **Route of administration:** *Oral*
- ***Formulation:** *disintegrating tablet*
- **Dosage:** *75 and 50 mg*
- **Regimen:** *list frequency of dosage administration*

**If the dosage form is powder for oral suspension; provide information on storage statement and concentration after reconstitution (e.g. with water, juice or apple sauce etc.)*

Types of Studies/ Study Design:

Example:

Study 1: Multi- center, randomized, active controlled double blind study to evaluate the safety and efficacy of (drug name, concentration, form etc) DRUG administered twice daily for the treatment of patients with disease x.

Study 2: PK and safety study of (drug name, concentration, form etc) DRUG in patients with disease x.

Age group and population in which study/ies was/were performed:

Example:

Study 1: patients aged X to Y years.

Study 2: sufficient number of patients to adequately characterize the pharmacokinetics in the above age groups.

Number of patients studied or power of study achieved:

Example:

Study 1: X patients in each treatment arm and was powered to show that (drug name, concentration, form etc) DRUG is not inferior to the active comparator. 50% were females and 25% were less than 3 years.

Study 2: powered and structured to detect a 30% change in (drug name, concentration, form etc) DRUG clearance and other relevant pharmacokinetic parameters. The study included at least X evaluable patients. .

Entry criteria:

This section should list pertinent inclusion/exclusion criteria.

Example:

Entry criteria: Pediatric patients with disease x diagnosed with laboratory test of LFTs

Patients had a negative pregnancy test if female.

Clinical endpoints:

Example:

Study 1: Clinical outcome and safety were the primary endpoints.

Study 2: The primary pharmacokinetic analysis of (drug name, concentration, form etc) DRUG attempted to include all the patients in the study with determination of the following parameters: single dose and steady state AUC, Cmax, Tmax, and CL/F

Statistical information (statistical analyses of the data performed):

This section should list the statistical tests conducted.

Example:

Study 1 - two-sided 95% confidence interval (CI) of treatment difference in improvement rates were within 25% of the control's response rate.

Study 2: descriptive statistical methods for AUC, C max, Tmax, CI/F and compared to adults.

Timing of assessments:

Example:

Baseline, week 2, week 6, and end of treatment

Division comments and conclusions (Summary of Safety and Efficacy)

Provide language Review Division is proposing for the appropriate sections of the label if different from sponsor-proposed language.

Reference ID: 3707718

Reference ID: 3773847

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

/s/

CHRISTINE H CHUNG
02/25/2015

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION¹

NDA # 206756 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Stiolto Respimat Established/Proper Name: tiotropium/olodaterol Dosage Form: Inhalation Spray		Applicant: Boehringer Ingelheim Agent for Applicant (if applicable):
RPM: Christine Ford		Division of Pulmonary, Allergy, and Rheumatology Products
NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p>For ALL 505(b)(2) applications, two months prior to EVERY action:</p> <ul style="list-style-type: none"> • Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <ul style="list-style-type: none"> <input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i> <p>Date of check:</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>
Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>5/22/2015</u> • Previous actions <i>(specify type and date for each action taken)</i> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR <input checked="" type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: Standard Priority
 Chemical classification (new NDAs only): 4
(confirm chemical classification at time of approval)

Fast Track Rx-to-OTC full switch
 Rolling Review Rx-to-OTC partial switch
 Orphan drug designation Direct-to-OTC
 Breakthrough Therapy designation

NDAs: Subpart H Accelerated approval (21 CFR 314.510)
 Restricted distribution (21 CFR 314.520)
 Subpart I Approval based on animal studies

BLAs: Subpart E Accelerated approval (21 CFR 601.41)
 Restricted distribution (21 CFR 601.42)
 Subpart H Approval based on animal studies

Submitted in response to a PMR
 Submitted in response to a PMC
 Submitted in response to a Pediatric Written Request

REMS: MedGuide
 Communication Plan
 ETASU
 MedGuide w/o REMS
 REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 <i>(approvals only)</i>	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications <i>(approvals only)</i>	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list <i>(approvals only)</i>	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
Copies of all action letters <i>(including approval letter with final labeling)</i>	Action(s) and date(s) Approval 5/21/15
Labeling	
❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	
• Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i>	<input checked="" type="checkbox"/> Included
• Original applicant-proposed labeling	<input type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling <i>(write submission/communication date at upper right of first page of each piece)</i>	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input checked="" type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
• Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i>	<input checked="" type="checkbox"/> Included
• Original applicant-proposed labeling	<input type="checkbox"/> Included
❖ Labels (full color carton and immediate-container labels) <i>(write submission/communication date on upper right of first page of each submission)</i>	
• Most-recent draft labeling	<input checked="" type="checkbox"/> Included
❖ Proprietary Name	
• Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i>	9/2/14 8/29/14
• Review(s) <i>(indicate date(s))</i>	
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: <input type="checkbox"/> None 1/27/15 DMEPA: <input type="checkbox"/> None 9/3/14 DMPP/PLT (DRISK): <input type="checkbox"/> None 2/17/15 OPDP: <input type="checkbox"/> None 2/18/15 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Product Quality <input checked="" type="checkbox"/> None Other: <input type="checkbox"/> None
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting <i>(indicate date of each review)</i>	5/13/15
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary <i>(signed by Division Director)</i>	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

<ul style="list-style-type: none"> This application is on the AIP <ul style="list-style-type: none"> If yes, Center Director's Exception for Review memo (<i>indicate date</i>) If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> Date reviewed by PeRC 3/11/2015 If PeRC review not necessary, explain: _____ 	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) (<i>do not include previous action letters, as these are located elsewhere in package</i>)	2015 – 5/20, 15, and 14, 4/15, 3/20 2014- 10/29, 23, and 2, 8/4, 6/11
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	None
❖ Minutes of Meetings	
<ul style="list-style-type: none"> If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> No mtg 9/9/2013
<ul style="list-style-type: none"> EOP2 meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> No mtg 7/29/11 CMC 7/20/2011
<ul style="list-style-type: none"> Mid-cycle Communication (<i>indicate date of mtg</i>) 	<input type="checkbox"/> N/A 11/6/14
<ul style="list-style-type: none"> Late-cycle Meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> N/A 2/24/15
<ul style="list-style-type: none"> Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>) 	
• Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> Date(s) of Meeting(s) 	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 5/21/2015
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 4/16/15
PMR/PMC Development Templates (<i>indicate total number</i>)	<input checked="" type="checkbox"/> None
Clinical	
❖ Clinical Reviews	
<ul style="list-style-type: none"> Clinical Team Leader Review(s) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> No separate review CDTL review
<ul style="list-style-type: none"> Clinical review(s) (<i>indicate date for each review</i>) 	1/23/15, 7/15/14
<ul style="list-style-type: none"> Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	Page 97 of MOR dated 1/23/15
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> N/A

❖ Risk Management	
<ul style="list-style-type: none"> REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	<input type="checkbox"/> None 2/2/15
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input checked="" type="checkbox"/> None requested
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 4/30 and 1/23/15, 8/5/14
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 1/23/15, 7/23/14
❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
<ul style="list-style-type: none"> ADP/T Review(s) (<i>indicate date for each review</i>) Supervisory Review(s) (<i>indicate date for each review</i>) Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> No separate review <input type="checkbox"/> No separate review 1/29/15 <input type="checkbox"/> None 5/18, 1/28 & 1/23/2015, 6/30/14
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
<ul style="list-style-type: none"> Tertiary review (<i>indicate date for each review</i>) Secondary review (e.g., Branch Chief) (<i>indicate date for each review</i>) Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) 	<input checked="" type="checkbox"/> None <input checked="" type="checkbox"/> None <input type="checkbox"/> None 1/23/15 8/13 and 6/23/2014
Reviews by other disciplines/divisions/Centers requested by product quality review team (<i>indicate date of each review</i>)	<input type="checkbox"/> None Micro 7/8/14, 12/3/14 CDRH OC - 5/20/15, 10/29/14 (darfts dates)

❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	1/23/15 CMC review page 66
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> Facilities inspections (<i>action must be taken prior to the re-evaluation date</i>) (<i>only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i>)	<input checked="" type="checkbox"/> Acceptable 5/19/15 Re-evaluation date: 9/12/2015 <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

Day of Approval Activities

❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
• Finalize 505(b)(2) assessment	<input type="checkbox"/> Done
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	<input type="checkbox"/> Done (<i>Send email to CDER OND IO</i>)
❖ For products that need to be added to the flush list (generally opioids): <u>Flush List</u> • Notify the Division of Online Communications, Office of Communications	<input type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the "preferred" name	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done



Chunxue Bai, M.D., Ph.D.
Fudan University
Zhongshan Hospital
No. 180 Fenglin Road
Xuhui District, Shanghai, China 200032

Dear Dr. Bai:

Between September 8 and 12, 2014, Ms. Christine O'Leary and Rachelle Lubin, Pharm.D., representing the Food and Drug Administration (FDA), met with your staff to review your conduct of the following protocols performed for Boehringer Ingelheim:

-  (b) (4)
- Protocol 1237.6, "A Randomized, Double-Blind, Parallel Group Study to Assess the Efficacy and Safety of 52 Weeks of Once Daily Treatment of Orally Inhaled Tiotropium + Olodaterol Fixed Dose Combination (2.5 µg/5µg; 5 µg/5µg) (Delivered by the Respimat Inhaler) Compared with the Individual Components (2.5 µg and 5 µg Tiotropium, 5 µg Olodaterol) (Delivered by the Respimat Inhaler) in Patients with Chronic Obstructive Pulmonary Disease (COPD) [TOnado™2]," of investigational drug Tiotropium/Olodaterol (Respimat)

This inspection is a part of the FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to help ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

We understand that you conducted this study under a U.S. Investigational New Drug Application (IND) and thus, the conduct of the study is subject to the U.S. Code of Federal Regulations (CFR).

At the conclusion of the inspection, Ms. O'Leary and Dr. Lubin presented and discussed with you Form FDA 483, Inspectional Observations. We have reviewed the Form FDA 483, the establishment inspection report, and the documents submitted with the report. We acknowledge your September 22, 2014, written response to the inspection findings and note that you plan to implement corrective actions to prevent the recurrence of the inspection findings.

Please make appropriate corrections in your procedures to ensure that the findings noted during the inspection are not repeated in any ongoing or future studies.

We appreciate the cooperation shown to Investigator O’Leary and Dr. Lubin during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

{See appended electronic signature page}

Constance Cullity, M.D., M.P.H.
Branch Chief
Good Clinical Practice Compliance Oversight Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
Building 51, Room 5354
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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/s/

CONSTANCE CULLITY
05/20/2015



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

Date: May 15, 2015

To: Anna Wysowskyj, MBA Sr. Associate Director, Drug Regulatory Affairs	From: Christine Ford, R.Ph. Regulatory Project Manager
Company: Boehringer Ingelheim Pharmaceuticals, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: 203-798-4280	Fax number: 301-796-9728
Email: anna.wysowskyj@boehringer-ingelheim.com	Phone number: 301-796-3420
Subject: NDA 206756 Stiolto Respimat FDA labeling comments	

Total no. of pages including cover: 27

Comments: Please call or send an email to confirm receipt at christine.ford@fda.hhs.gov

Submit response no later than noon Tuesday, May 19, 2015

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-3420. Thank you.

We refer to Stiolto Respimat NDA 206756 and have the following labeling edits provided in the attached marked up label. Additional labeling changes may be forthcoming.

FDA edits were made as tracked changes to the clean version of your proposed labeling submitted May 1, 2015. We also have the following comment:

1. As we had discussed during the labeling teleconference on April 28, 2015,

(b) (4)

A large rectangular area of the document is redacted with a solid grey fill. The redaction covers the majority of the text in the first list item.

- 2.

(b) (4)

A large rectangular area of the document is redacted with a solid grey fill. The redaction covers the majority of the text in the second list item.

Any additional proposed changes you may have can be made in a similar fashion by using the clean Word version of the attached labeling and edit using tracked changes.

Submit revised draft labeling incorporating the requested changes to me via secure email at christine.ford@fda.hhs.gov by noon May 19, 2015. Your response will subsequently need to be submitted officially to the NDA.

If you have any questions, please contact me at 301-796-3420.

Drafted by: RDavi/5.7.2015
RLim/ 5.13.2015
ADurmowicz/ 5.15.2015
cford/ 5.15.2015

Initialed by: SBarnes/ 5.15.2015
RLim/ 5.15.2015

Finalized: cford/ 5.15.2015

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

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/s/

CHRISTINE H CHUNG
05/15/2015



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

Date: May 14, 2015

To: Anna Wysowskyj, MBA Sr. Associate Director, Drug Regulatory Affairs	From: Christine Ford, R.Ph. Regulatory Project Manager
Company: Boehringer Ingelheim Pharmaceuticals, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: 203-798-4280	Fax number: 301-796-9728
Email: anna.wysowskyj @boehringer-ingelheim.com	Phone number: 301-796-3420

Subject: NDA 206756 tiotropium/olodaterol Respimat
FDA request for information – Demographic subgroups

Total no. of pages including cover: 7

Comments: *Information requested as soon as possible but no later than cob*

Wednesday, May 20, 2015

Please call or send an email to confirm receipt at christine.ford@fda.hhs.gov

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-3420. Thank you.

Your NDA 206756 for Stiolto (tiotropium/olodaterol) Respimat is currently under review, and we are requesting your assistance in populating the attached tables.

As part of FDASIA 2012, information on demographic subgroups in clinical trials for newly-approved drugs (new molecular entities) and biologics will be made publicly available on www.fda.gov/drugtrialsnapshot.

The website will include information on study design, results of efficacy and safety studies, and whether there were any differences in efficacy and side effects within sex, race, and age subgroups. The website is not intended to replace or replicate the package insert (PI), which is intended for health care practitioners, and will contain the following:

- Information written in consumer-friendly language,
- “MORE INFORMATION” sections that provide more technical, data-heavy information,
- Information that focuses on subgroup data and analyses, and
- Links to the PI for the product and to the FDA reviews at Drugs@FDA.

Submit the requested information as an official response to the NDA as soon as possible but no later than close of business Wednesday, May 20, 2015.

If you have any questions, please contact Christine Ford at 301-796-3420.

Drafted by: PASE/ 5.4.2015
cford/ 5.6.2015

Initialed by: SBarnes/ 5.6.2015
RLim/ 5.6.2015
ADurmowicz/ 5.13.2015

Finalized: cford/ 5.14.2015

Table 6.1.1 Listing of Clinical Trials for the Efficacy Analysis

Study ID	No. of patients enrolled in T+O 5/5	No. of patients enrolled in Olo 5	No. of patients enrolled in Tio 5
1237.5			
1237.5			

Table 6.1.2-b. Baseline Demographics

Demographic Parameters	1237.5			1237.6			Total (N=)
	T+O 5/5 (N=) n (%)*	Olo 5 (N=) n (%)*	Tio 5 (N=) n (%)*	T+O 5/5 (N=) n (%)*	Olo 5 (N=) n (%)*	Tio 5 (N=) n (%)*	
Sex							
Male							
Female							
Age							
Mean years (SD)							
Median (years)							
Min, Max (years)							
Age Group							
<17 years							
>=17 - <65 years							
>=65 years							
>=75 years							
Race							
White							
Black or African American							
Asian							
American Indian or Alaska Native							
Native Hawaiian or Other Pacific Islander							
Other							
Ethnicity							
Hispanic or Latino							
Not Hispanic or Latino							
Region							
United States							
Rest of the World							
Canada							
South America							
Europe							
Asia							
Africa							

Source:

* Percentages are calculated based on the total number of subjects in the respective arm.

Table 6.1.7 Subgroup Analysis of Co-primary Endpoint, Trials 1237.5 and 1237.6 (separate table for each trial and each co-primary endpoint)

Subgroup	T+O 5/5		Olo 5		T+O 5/5 - Olo 5	95% CI		Tio 5		T+O 5/5 - Tio 5	95% CI	
	x (%)*	Total, n	x (%)*	Total, n		LL	UL	x (%)*	Total, n		LL	UL
Overall Response/All patients												
Sex												
Male												
Female												
Age Group												
>=17 - <65 years												
>=65 years												
>=75 years												
Race												
White												
Black or African American												
Asian												
American Indian or Alaska Native												
Native Hawaiian or Other Pacific Islander												
Other												
Ethnicity												
Hispanic or Latino												
Not Hispanic or Latino												
Region												
United States												
Rest of the World												
Canada												
South America												
Europe												
Asia												
Africa												

Source:

*Percentages are calculated based on the number of subjects in the subgroup per arm.

Table 7.5.3-a. Subgroup Analysis of AEs, Safety Population (2 trials pooled)

Subgroup	T+O 5/5		Olo 5		Tio 5	
	x (%)*	Total, n	x (%)*	Total, n	x (%)*	Total, n
Any TEAEs						
Sex						
Male						
Female						
Age Group						
>=17 - <65 years						
>=65 years						
>=75 years						
Race						
White						
Black or African American						
Asian						
American Indian or Alaska Native						
Native Hawaiian or Other Pacific Islander						
Other						
Ethnicity						
Hispanic or Latino						
Not Hispanic or Latino						
Region (
United States						
Rest of the World						
Canada						
South America						
Europe						
Asia						
Africa						

Source:

* Percentages are calculated based on the number of subjects in the subgroup per arm.

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/s/

CHRISTINE H CHUNG
05/14/2015



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

Date: April 15, 2015

To: Anna Wysowskyj, MBA Sr. Associate Director, Drug Regulatory Affairs	From: Christine Ford, R.Ph. Regulatory Project Manager
Company: Boehringer Ingelheim Pharmaceuticals, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: 203-798-4280	Fax number: 301-796-9728
Email: anna.wysowskyj@boehringer-ingelheim.com	Phone number: 301-796-3420
Subject: NDA 206756 Stiolto Respimat FDA labeling comments	

Total no. of pages including cover: 26

Comments: Please call or send an email to confirm receipt at christine.ford@fda.hhs.gov

Submit response no later than close of business April 24, 2015

Document to be mailed: YES NO

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We refer to Stiolto Respimat NDA 206756 and have the following labeling edits provided in the attached marked up label. Additional labeling changes may be forthcoming.

FDA edits were made as tracked changes to the clean version of your proposed labeling submitted March 31, 2015. We also have the following comment:

We have removed the  (b) (4)


Any additional proposed changes you may have can be made in a similar fashion by using the clean Word version of the attached labeling and edit using tracked changes.

Submit revised draft labeling incorporating the requested changes to me via secure email at christine.ford@fda.hhs.gov by close of business (COB) April 24, 2015. Your response will subsequently need to be submitted officially to the NDA.

If you have any questions, please contact me at 301-796-3420.

Drafted by: RLim, ADurmowicz/ 4.14.2015
cford/ 4.15.2015

Initialed by: SBarnes/ 4.15.2015

Finalized: cford/ 4.15.2015

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

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/s/

CHRISTINE H CHUNG
04/15/2015

**PeRC Meeting Minutes
March 11, 2015**

PeRC Members Attending:

Lynne Yao

Rosemary Addy (only reviewed **Non Responsive**)

Jane Inglese

Hari Cheryl Sachs

Wiley Chambers

Tom Smith

Karen Davis-Bruno

Peter Starke

Andrew Mulberg

Gregory Reaman

Daiva Shetty

Julia Pinto

Freda Cooner

Lily Mulugeta

Nisha Jain (only reviewed **Non Responsive**)

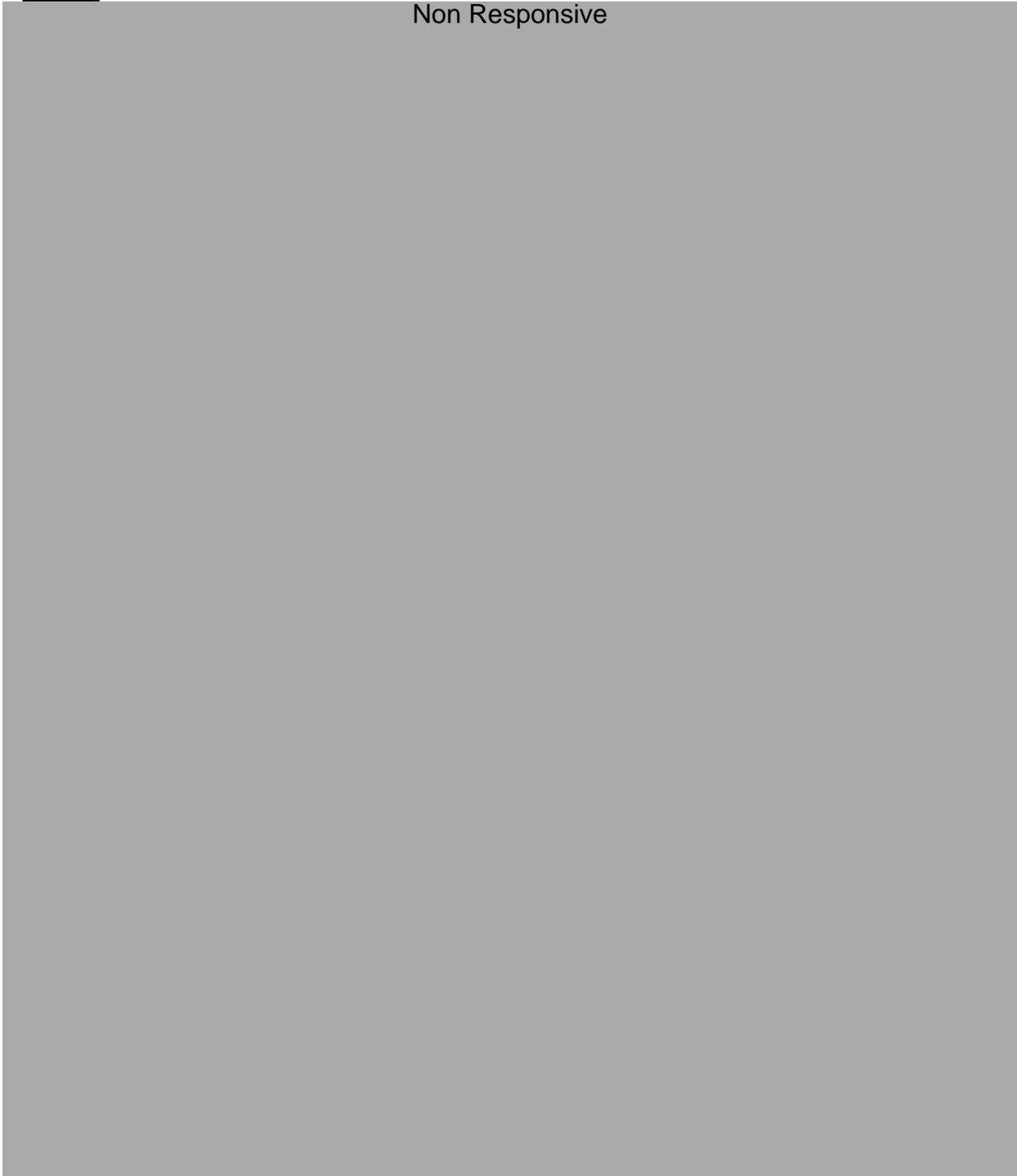
Barbara Buch (only reviewed **Non Responsive**)

Adrienne Hornatko-Munoz (only reviewed **Non Responsive**)

Dianne Murphy

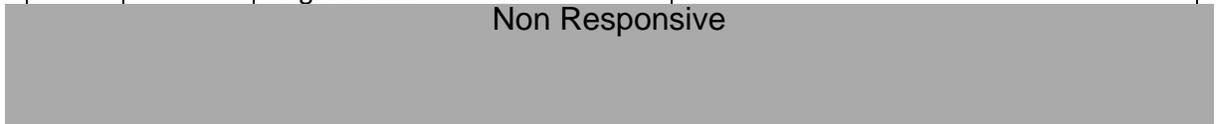
Agenda

Non Responsive



NDA	206756	Stiolto Respimat (tiotropium/olodaterol) Full Waiver *Agreed iPSP	Treatment of chronic obstructive pulmonary disease
-----	--------	--	---

Non Responsive



4 Pages have been Withheld in Full as Non Responsive immediately following this page.

Non Responsive

Stiolto Respimat (tiotropium/olodaterol) Full Waiver

- NDA 206756 seeks marketing approval for Stiolto Respimat (tiotropium/olodaterol) for treatment of chronic obstructive pulmonary disease.
- The application triggers PREA as directed to a new active ingredient.
- The application has a PDUFA goal date of May 22, 2015.
- *PeRC Recommendations:*
 - The PeRC agreed with a full waiver because studies would be impossible or highly impracticable.

1 Page has been Withheld in Full as Non Responsive immediately following this page.

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/s/

JANE E INGLESE
03/23/2015



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

Date: March 20, 2015

To: Anna Wysowskyj, MBA Sr. Associate Director, Drug Regulatory Affairs	From: Christine Ford, R.Ph. Regulatory Project Manager
Company: Boehringer Ingelheim Pharmaceuticals, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: 203-798-4280	Fax number: 301-796-9728
Email: anna.wysowskyj @boehringer-ingelheim.com	Phone number: 301-796-3420
Subject: NDA 206756 Stiolto Respimat FDA labeling comments	

Total no. of pages including cover: 32

Comments: Please call or send an email to confirm receipt at christine.ford@fda.hhs.gov

Submit response no later than close of business Monday, March 30, 2015

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

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We refer to Stiolto Respimat NDA 206756 and have the following labeling comments provided in the attached marked up label. Additional labeling changes may be forthcoming.

FDA edits were made as tracked changes to the clean version of your proposed label submitted May 22, 2014. Any additional proposed changes you may have can be made in a similar fashion by using the clean Word version of the attached PI and edit using tracked changes.

Submit revised draft labeling incorporating the requested changes to me via secure email at christine.ford@fda.hhs.gov by close of business (COB) March 30, 2015. Your response will subsequently need to be submitted officially to the NDA.

If you have any questions, please contact me at 301-796-3420.

Drafted by: Review and labeling consult teams/ 3.18.2015
cford/ 3.19.2015

Initialed by: SBarnes/ 3.19.2015
RLim, ADurmowicz/ 3.20.2015

Finalized: cford/ 3.20.2015

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

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/s/

CHRISTINE H CHUNG
03/20/2015



NDA 206756

MID-CYCLE COMMUNICATION

Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

Attention: Anna Wysowskyj, MBA
Senior Associate Director, Regulatory Affairs

Dear Ms. Wysowskyj:

Please refer to your New Drug Application (NDA) dated and received May 22, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Stiolto Respimat (tiotropium bromide and olodaterol) Inhalation Spray.

We also refer to the teleconference between representatives of your firm and the FDA on November 6, 2014. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call me at (301) 796-3420.

Sincerely,

{See appended electronic signature page}

Christine Ford, R.Ph.
CDR, U.S. Public Health Service
Sr. Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: November 6, 2014

Application Number: NDA 206756

Product Name: Stiolto Respimat (tiotropium bromide and olodaterol) Inhalation Spray

Indication: Chronic obstructive pulmonary disease (COPD)

Applicant Name: Boehringer Ingelheim Pharmaceuticals, Inc. (BI)

Meeting Chair: Anthony Durmowicz, Cross-Discipline Team Leader

Meeting Recorder: Christine Ford, Regulatory Project Manager

FDA ATTENDEES:

Anthony Durmowicz, MD, Clinical Team Leader, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

Robert Lim, MD, Clinical Reviewer, DPARP

Christine Ford, RPh, Regulatory Project Manager, DPARP

Eric Duffy, PhD, Director, Division of New Drug Quality Assessment (DNDQA) III

Eugenia Nashed, PhD, CMC Reviewer, DNDQA III

Craig Bertha, PhD, CMC Lead, DNDQA III

Julia Pinto, PhD, Acting Branch Chief, DNDQA III, Branch VIII

EASTERN RESEARCH GROUP ATTENDEES:

(b) (6) Independent Assessor

APPLICANT ATTENDEES:

Dr. Michael Kraft - Head Global Regulatory Affairs

Dr. Sabine Luik - Head US Medical and Regulatory Affairs

Dr. Joanne Palmisano - Head US Regulatory Affairs

Jeff Snyder - US Regulatory Affairs Respiratory

Dr. Bernd Disse - Therapeutic Area Head Medicine Respiratory

Dr. Tunde Otulana - Head US Medical Affairs

Dr. Daniel McBryan - US Medical Affairs Respiratory

Dr. Claude Petit - Head US Clinical Data Management

Dr. Alan Hamilton - Clinical Program Head

Dr. Kay Tetzlaff - Clinical Safety

Stella Waitere-Wijker - Clinical Operations

Dr. Lars Groenke - Global Medical Affairs

Dr. Emmanuelle Clerisme-Beaty - US Medical Affairs

Dr. Yihua Zhao - Statistics

Lawrence Korducki - Statistics

Dr. Thomas Bethke - Drug Safety
Dr. Ulrich Bothner - Drug Safety
Dr. Lazaro Loaiza - Drug Safety
Dr. Tanjew Dittgen - R&D Project Management
Dr. Annerose Mauz - Toxicology
Dr. Christina Kunz - Clinical PK
Annette Wasmund - Global Regulatory Affairs
Anna Wysowskyj - US Regulatory Affairs
James Webb - US Regulatory Affairs CMC
Dr. Nadja Oellers - International Project Leader

INTRODUCTION:

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

SIGNIFICANT ISSUES:

No significant issues have been identified to date.

INFORMATION REQUESTS:

Except for the October 29, 2014, information request already requested by the CDRH Office of Compliance (OC), at this time there are no additional information requests.

Regarding the October 29, 2014, information request, FDA commented that historically regulations for combination product (drug/device) may not have been fully applied to inhalers such as the Respimat. Going forward however, 21 CFR Part 4 and Part 820 will have to be addressed since the Agency considers Respimat inhalation spray a true (factual) drug-device combination product. The FDA explained that CDRH OC first completes a desk review of the NDA documents to determine if a physical inspection is needed and as background information for the inspection. FDA recommended that BI provide responses to the information requested in a timely manner. A brief response for each for the information request from CDRH OC would be acceptable. Any questions can be addressed through the OND or ONDQA Project Managers.

MAJOR SAFETY CONCERNS/RISK MANAGEMENT:

There are no major safety concerns identified at this time, and there is currently no need for a REMS.

ADVISORY COMMITTEE MEETING:

There are no plans at this time for an AC meeting.

LATE-CYCLE MEETING (LCM)/OTHER PROJECTED MILESTONES:

LCM is scheduled for February 24, 2015, and the PDUFA goal date is May 22, 2015.

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/s/

CHRISTINE H CHUNG
12/05/2014

Liu, Youbang

From: Liu, Youbang
Sent: Wednesday, October 29, 2014 3:20 PM
To: 'anna.wysowskyj@boehringer-ingenelheim.com'
Subject: Information Request for NDA 206756

Importance: High

NDA 206756

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Anna Wysowskyj
Senior Associate Director
900 Ridgebury Rd., PO Box 368
Ridgefield, CT 06877

Dear Ms. Wysowskyj:

We are reviewing the Chemistry, Manufacturing and Controls section of your submission for NDA 206756, Stiolto Respimat[®] (tiotropium and olodaterol) Inhalation Spray, received May 22, 2014. The following deficiencies have been identified 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>

Please acknowledge the receipt of this email and provide the requested information by November 12, 2014.

Sincerely,

Youbang Liu, Ph.D.
Regulatory Project Manager
Division III, ONDQA/OPS/CDER/FDA
10903 New Hampshire Avenue
Building 21, Room 2525
Silver Spring, MD 20903
Phone: (301) 796-1926

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/s/

YOUBANG LIU
10/29/2014



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

Date: October 23, 2014

To: Anna Wysowskyj, MBA Sr. Associate Director, Drug Regulatory Affairs	From: Christine Ford, R.Ph. Regulatory Project Manager
Company: Boehringer Ingelheim Pharmaceuticals, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: 203-798-4280	Fax number: 301-796-9728
Email: anna.wysowskyj @boehringer-ingelheim.com	Phone number: 301-796-3420
Subject: NDA 206756 tiotropium/olodaterol Respimat FDA request for information – Clinical	

Total no. of pages including cover: 3

Comments: *Information requested by no later than cob Tuesday, November 4, 2014*

Please call or send an email to confirm receipt at christine.ford@fda.hhs.gov

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-3420. Thank you.

Your NDA 206756 for Stiolto (tiotropium/olodaterol) Respimat is currently under review, and we have the following request for information:

Provide a table summarizing only the non-fatal serious adverse events from trials 1237.5 and 1237.6. Use a format similar to table 2.5.4 from the summary of clinical safety supplement (pages 1333 – 1339).

Submit the requested information as an official response to the NDA no later than close of business Tuesday, November 4, 2014, or provide a timeline for when the information will be submitted.

If you have any questions, please contact Christine Ford at 301-796-3420.

Drafted by: RLim/ 10.22.2014
cford/ 10.23.2014

Initialed by: ARamsey for SBarnes/ 10.23.2014
ADurmowicz/ 10.23.2014

Finalized: cford/ 10.23.2014

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/s/

CHRISTINE H CHUNG
10/23/2014



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

Date: October 2, 2014

To: Anna Wysowskyj, MBA Sr. Associate Director, Drug Regulatory Affairs	From: Christine Ford, R.Ph. Regulatory Project Manager
Company: Boehringer Ingelheim Pharmaceuticals, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: 203-798-4280	Fax number: 301-796-9728
Email: anna.wysowskyj @boehringer-ingelheim.com	Phone number: 301-796-3420

Subject: NDA 206756 tiotropium/olodaterol Respimat
FDA request for information – Product quality microbiology

Total no. of pages including cover: 3

Comments: *Information requested by no later than Tuesday, October 14, 2014*

Please call or send an email to confirm receipt at christine.ford@fda.hhs.gov

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-3420. Thank you.

Your NDA 206756 for Stiolto (tiotropium/olodaterol) Respimat is currently under review, and we have the following request for information:

Provide the following information or a reference to its location in the NDA submission.

1. We refer to the media fill summary provided in Module 3.2.P.3.5 Section 10. Provide the following information for the 2013 and any 2014 media fills.
 - a. Provide the number of units filled, the number of units rejected (with a brief reason for the rejection), the number of units (b) (4), and the number of positive units.
 - b. Indicate whether any visual inspection of media fill units occurs prior to (b) (4). We note a (b) (4) occurs for commercial product.
 - c. Provide a more detailed description of the incomplete nature of the April 2013 media fill and the role of the June 2013 media fill with respect to the erroneously rejected integral units. Describe the April investigation and any corrective actions.
2. We refer to the sterility test verification studies conducted by (b) (4) described in document q00218284-01. Indicate which drug product batches were utilized in these verification studies.

Submit the requested information as an official response to the NDA no later than Tuesday, October 14, 2014, or provide a timeline for when the information will be submitted.

If you have any questions, please contact Christine Ford at 301-796-3420.

Drafted by: Microbiology - JCole, BRiley/ 10.2.2014
cford/ 10.2.2014

Initialed by: SBarnes/ 10.2.2014

Finalized: cford/ 10.2.2014

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/s/

CHRISTINE H CHUNG
10/02/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 206756

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Rd
P.O. Box 368
Ridgefield, CT 06877

ATTENTION: Anna Wysowskyj, MBA
Senior Associate Director, Regulatory Affairs

Dear Ms. Wysowskyj:

Please refer to your New Drug Application (NDA) dated May 22, 2014, received May 22, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tiotropium Bromide and Olodaterol Inhalation Spray, 2.5 mcg/2.5 mcg per inhalation.

We also refer to your June 13, 2014, correspondence, received June 13, 2014, requesting review of your proposed proprietary name, Stiolto Respimat.

We have completed our review of the proposed proprietary name, Stiolto Respimat and have concluded that it is acceptable.

If any of the proposed product characteristics as stated in your June 13, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Nichelle Rashid, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3904. For any other information regarding this application, contact Christine Chung, Regulatory Project Manager in the Office of New Drugs, at (301) 796-3420.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES on behalf of KELLIE A TAYLOR
09/02/2014



NDA 206756

**FILING COMMUNICATION -
NO FILING REVIEW ISSUES IDENTIFIED**

Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

Attention: Anna Wysowskyj, MBA
Senior Associate Director, Regulatory Affairs

Dear Ms. Wysowskyj:

Please refer to your New Drug Application (NDA) dated and received May 22, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Stiolto (tiotropium and olodaterol) Respimat Inhalation Spray

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. This application is also subject to the provisions of "the Program" under the Prescription Drug User Fee Act (PDUFA) V (refer to <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>). Therefore, the user fee goal date is May 22, 2015.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by February 1, 2015. In addition, the planned date for our internal mid-cycle review meeting is during the week of October 19, 2014. We are not currently planning to hold an advisory committee meeting to discuss this application.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We request that you submit the following information:

Provide the sterility test method verification studies to support the proposed formulations.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). We encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), Medication Guide and Instruction or Use. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), Medication Guide, and Instructions for Use, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, call Christine Chung, Regulatory Project Manager, at (301) 796-3420.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

BADRUL A CHOWDHURY
08/04/2014



NDA 206756

NDA ACKNOWLEDGMENT

Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

Attention: Anna Wysowskyj, MBA
Senior Associate Director, Regulatory Affairs

Dear Ms. Wysowskyj:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: tiotropium+olodaterol RESPIMAT inhalation spray

Date of Application: May 22, 2014

Date of Receipt: May 22, 2014

Our Reference Number: NDA 206756

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on **July 21, 2014**, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary, Allergy, and Rheumatology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (301) 796-3420.

Sincerely,

{See appended electronic signature page}

Christine Chung, R.Ph.
CDR, U.S. Public Health Service
Program Coordinator
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

CHRISTINE H CHUNG
06/11/2014



IND 76397

**MEETING REQUEST-
WRITTEN RESPONSES**

Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877-0368

Attention: Anna Wysowskyj, MBA
Sr. Associate Director, Regulatory Affairs

Dear Ms. Wysowskyj:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for tiotropium and olodaterol Respimat Inhalation Spray.

We also refer to your July 11, 2013, correspondence requesting a pre-NDA meeting Written Responses Only (WRO) to receive comments on the format and content of the planned NDA.

Further reference is made to our Meeting Granted letter dated July 30, 2013, wherein we stated that written responses to your questions would be provided in lieu of a meeting, as requested.

The enclosed document constitutes our written responses to the questions contained in your August 13, 2013, background package.

If you have any questions, call me at (301) 796-3420.

Sincerely,

{See appended electronic signature page}

Christine Chung, R.Ph.
CDR, U.S. Public Health Service
Program Coordinator
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Written Responses



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

WRITTEN RESPONSES

Meeting Type: Type B
Meeting Category: Pre-NDA

Application Number: IND 76397
Product Name: tiotropium and olodaterol Respimat Inhalation Spray
Indication: COPD
Sponsor/Applicant Name: Boehringer Ingelheim Pharmaceuticals, Inc. (BI)
Regulatory Pathway: 505(b)(1)

BACKGROUND:

Tiotropium is a long-acting, inhaled anticholinergic developed for bronchodilator treatment in patients with chronic obstructive pulmonary disease (COPD). Olodaterol is a long-acting β_2 -adrenoceptor agonist also for maintenance bronchodilator treatment of airflow obstruction in patients with COPD. BI is developing a fixed-dose combination product 'tiotropium+olodaterol RESPIMAT solution for inhalation (Tio+Olo FDC) and requested a pre-NDA meeting Written Responses Only (WRO) to receive comments on the format and content of the planned NDA.

The briefing package was received August 13, 2013.

QUESTIONS AND PRELIMINARY RESPONSES

BI's questions in *italics font* are followed by the Division's responses in normal font.

FDA Introductory Comment:

We note that both monocomponents of the Tio+Olo FDC [Tiotropium Respimat (TR) and Olodaterol Respimat (OR)] received Complete Responses after their last review cycles. TR was given a Complete Response due to safety issues. OR was given a Complete Response due to current Good Manufacturing Practices (cGMP) deficiencies. Failure to resolve the above deficiencies for both monocomponents will negatively impact the approvability of your proposed tiotropium/olodaterol combination product.

To support inclusion of health-related quality of life as measured by the St. George's Respiratory Questionnaire in the CLINICAL TRIALS section of the product label, you must provide data from adequate, and well-controlled trials in which the improvement in SGRQ total score meets the MCID of -4 in favor of your proposed product.

Question 1: The proposed Tio+Olo FDC NDA Table of Contents is provided in Appendix 1. Does the Division have any comments on the overall format or content of the NDA?

FDA response:

We do not have additional comments.

Question 2: *Because no REMS was required for Spiriva® HandiHaler® and none is expected for either tiotropium RESPIMAT or olodaterol RESPIMAT, BI does not plan on including a REMS in the Tio+Olo FDC NDA unless the ongoing Phase III studies identify unexpected and significant safety signals.*

Does the Division agree with BI's current plan not to submit a REMS for Tio+Olo FDC?

FDA response:

We agree, pending review of data for the combination product.

Question 3: *Does the Division have any comments regarding the organization and/or proposed content of Section 2.7.1?*

FDA response:

We do not have any additional comments.

Question 4: *Does the Division have any comments regarding the organization and/or proposed content of Section 2.7.2?*

FDA response:

We do not have any additional comments.

Question 5: *Does the Division agree with using the same approach to complying with the ISE requirements as was used for the olodaterol RESPIMAT NDA?*

FDA response:

Your approach is acceptable.

Question 6: *Does the Division agree with the planned subgroup efficacy analyses? Does the Division recommend analyzing any other subgroups?*

FDA response:

Your proposed subgroups are reasonable. Provide subgroup analyses and tests of interactions for sex, age, race, and region for each of the 52-week, parallel-group trials, 1237.5 and 1237.6.

Question 7: *Based on the mock Section 2.7.3 SCE in Appendix 5, the mock SCE Supplement document in Appendix 6, and the Module 5 table of contents in Appendix 1, does the Division have any additional comments on the proposed overall approach to the analysis of efficacy?*

FDA response:

We do not have any additional comments.

Question 8: *Does the Division agree with using the same approach to complying with the ISS requirements as was used for the olodaterol RESPIMAT NDA?*

FDA response:

This approach appears reasonable.

Question 9: *Does the Division agree with the planned subgroup safety analyses? Does the Division recommend analyzing any other subgroups?*

FDA response:

Your proposed subgroups are reasonable.

Question 10: *For other inhalation product development programs the Division has asked BI to provide information on administration-related acute bronchospasm.* (b) (4)

(b) (4)

FDA response:

(b) (4) Include an analysis of administration related bronchospasm. (b) (4)

(b) (4)

Question 11:

(b) (4)

(b) (4)

FDA response:

(b) (4)

Question 12: *MedDRA Versions: Does the Division agree with this approach?*

FDA response:

This appears reasonable.

Question 13: *Adjudication of Serious Adverse Events: Does the Division have any comments on BI's SAE adjudication charter?*

FDA response:

We do not have comments on your adjudication charter.

Question 14: *Format and Content: Does the Division have any comments on BI's overall approach to the safety analyses?*

FDA response:

In your SAE tables for your 52-week trials, include all SAEs that occur in ≥ 2 patients.

Question 15: *CMC- A mock Module 3 Table of Contents is provided in Appendix 1. An overview of Module 3 is provided in Appendix 10.*

Does the Division agree with the proposed approach to Module 3, including the resubmission of certain tiotropium information for reviewer convenience?

FDA response:

Your proposed general approach to the submission of Module 3 appears reasonable. However, we do not exclude the possibility of requesting further information during the NDA review.

In addition to referencing DMF (b) (4) for the CMC information of tiotropium drug substance and the information you already planned to include, also include information related to the release testing of the drug substance before it is used for drug product manufacturing, such as how frequent and what methods you will use. If the methods are exactly the same as those used in the DMF and validated, you need to clearly document it in the NDA.

In the pharmaceutical development section, provide data that demonstrate that there is



that there is assurance that the resulting clinical/clinical pharmacology data will be appropriate to allow the Agency to assess whether the combination drug product has substantial activity and provides greater than additive activity, or a more durable response compared to the individual monotherapy drug products alone.

Question 16: *Nonclinical- As discussed with the Division during the End of Phase II Meeting, based on the nonclinical safety profiles of the tiotropium and olodaterol monoproducts, a limited nonclinical program was conducted with Tio+Olo FDC.*

Does the Division have any comments on the proposed Module 4?

FDA response:

No, we do not have any comments on the proposed Module 4.

Question 17: *Clinical- A mock Table of Contents for Module 5 and the Section 5.2 Table of Studies for the Tio+Olo FDC NDA are provided in Appendix 1 and Appendix 4, respectively. Does the Division have any comments on either document?*

FDA response:

We do not have any additional comments.

Question 18: *An NDA eSubmission Plan is included in Appendix 11. The plan includes information on the formatting of the clinical trial datasets in the eCTD. Does the Division have any comments on the details of the plan?*

FDA response:

We do not have additional comments.

Question 19: *Pursuant to 314.50(f)(2) BI will provide CRFs only for patients who were randomized and received at least one dose of study drug and either died or discontinued study drug due to an adverse event. BI will provide additional CRFs if requested by the Division during the NDA review. Does the Division agree with this approach?*

FDA response:

This approach appears reasonable.

Question 20: *ECGs- Does the Division agree with the handling of the ECG data in the NDA? Does the Division agree that uploading of ECG data to the ECG Warehouse is not required?*

FDA response:

This appears reasonable. While not required, we encourage you to submit your ECG data to the ECG Warehouse

Question 21: *4-month Safety Update: Does the Division agree with this approach?*

FDA response:

This appears reasonable.

Question 22: *Summary Level Clinical Site Data-*

(b) (4)

(b) (4)

FDA response:

We do not agree. The application should be complete at the time of submission; provide the Summary Level Clinical Site Data with the NDA submission.

Question 23: *Advisory Committee Meeting- Can the Division comment on whether BI should anticipate a PADAC meeting for this submission?*

FDA response:

We do not anticipate a PADAC meeting provided that safety concerns with the tiotropium Respimat product are resolved.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of

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administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting held on or after November 6, 2012. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the following labeling review resources: the Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products, labeling guidances, and a sample tool illustrating the format for Highlights and Contents (Table of Contents) available at: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>.

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/s/

CHRISTINE H CHUNG
09/09/2013



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Meeting Type: Type B
Meeting Category: End of Phase 2 (non CMC)
Meeting Date and Time: July 20, 2011
Meeting Location: White Oak Campus Bldg 22
Application Number: IND 76397
Product Name: olodaterol/tiotropium Respimat
Received Briefing Package June 20, 2011
Sponsor Name: Boehringer Ingelheim
Meeting Requestor: Damon Daulerio, M.B.A.
Meeting Chair: Badrul Chowdhury, M.D., Ph.D.
Meeting Recorder: Eunice Chung-Davies, Pharm.D.
Meeting Attendees:

FDA Attendees

Badrul Chowdhury, M.D., Ph.D., Director, Division of Pulmonary, Allergy, and Rheumatology Products

Sally Seymour, M.D., Deputy Director for Safety, Division of Pulmonary, Allergy, and Rheumatology Products

Brian Porter, M.D., Ph.D., M.P.H., Primary Clinical Reviewer, Division of Pulmonary, Allergy, and Rheumatology Products

Susan Limb, M.D., Clinical Team Leader, Division of Pulmonary, Allergy, and Rheumatology Products

Ruthanna Davi, Ph.D., Biometrics Reviewer, Division of Biometrics II

Joan Buenconsejo, Ph.D., Acting Biometrics Team Leader, Division of Biometrics II

Partha Roy, Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology II

Ping Ji, Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology II

Eunice Chung-Davies, Pharm.D., Sr. Regulatory Management Officer, Division of Pulmonary, Allergy, and Rheumatology Products

Sponsor Attendees

Joanne Palmisano, MD, VP, Drug Regulatory Affairs

Jeff Snyder, Executive Director, Drug Regulatory Affairs

Damon Daulerio, MBA, Associate Director, Drug Regulatory Affairs

Anna Wysowskyj, Senior Associate Director, Drug Regulatory Affairs

Annette Wasmund, Associate Director, Drug Regulatory Affairs

Nadja Oellers, PhD, International Project Leader

Bernd Disse, MD, PhD, Therapeutic Area Head, Respiratory Medicine

Alan Hamilton, PhD, Medical Project Leader (COPD)

Shailendra Menjoge, PhD Distinguished Biostatistician

Larry Korducki, MS, Project Statistician

Christina Kunz, PhD, Project Clinical Pharmacokineticist, Translational Medicine

Christel Schmelzer, PhD, Internal CMC Consultant, Germany

Dietrich Schuetze, PhD, Project Toxicologist, Department of Nonclinical Drug Safety, Germany

Christopher D. Corsico, MD, MPH, Senior VP, Medicine & Regulatory, US Regional Medical Director, NA

1.0 BACKGROUND

Mr. Damon Daulerio of BI requested a Type B, End-of-Phase 2 (non CMC) meeting on May 9, 2011. The meeting was granted on May 18, 2011. The briefing package was received on June 20, 2011. Preliminary Comments (in italics) in response to the sponsor's questions (in bold italics) were sent to the sponsor on July 18, 2011. Any discussion from the July 20, 2011, face to face meeting is in normal font. Any post meeting notes are in bold font.

QUESTIONS AND RESPONSES AND DISCUSSION

Introductory Comment:

The briefing materials state that

(b) (4)

(b) (4)

(b) (4) *Therefore, we recommend that the combination product NDA follow the completion of the ongoing large safety trial for tiotropium, TIOSPIR (205.452), and the submission and review of the tiotropium Respimat Complete Response. An approval of the olodaterol and tiotropium monotherapies will facilitate the subsequent review of the combination product. Conversely, any issues identified with the monotherapies may impact the viability of the combination product.*

With respect to the olodaterol monocomponent, we note that development and approval of other long-acting beta-agonists (LABA) in COPD have been generally preceded by development in asthma. As discussed during the July 7, 2010, teleconference, we expect that assessment of dose and dosing frequency in a bronchoresponsive asthma population will inform dose selection in COPD. Based on the limited summary information provided, we are unable to confirm whether the proposed olodaterol 5 mcg dose and once-daily dosing frequency are supported. Initiating Phase 3 trials is risky if dose ranging is incomplete.

Discussion:

In light of the responses provided in the Introductory Comments, Question 1e and Question 5, the sponsor asked whether there is an opportunity for a parallel review of the two NDAs (tiotropium Respimat and tiotropium/olodaterol combination) if the TIOSPIR results are submitted at the time of the tiotropium/olodaterol combination NDA submission. The Division stated that it would be ideal if the NDA for olodaterol RESPIMAT and the Complete Response for tiotropium RESPIMAT were reviewed prior to the combination olodaterol + tiotropium RESPIMAT NDA. The Division stated that the results of the TIOSPIR trial alone in the absence of a Complete Response for tiotropium RESPIMAT may be insufficient to characterize the safety and efficacy of tiotropium monocomponent of the combination.

(b) (4)

(b) (4)

(b) (4) but the
Division acknowledged that this approach would be possible.

(b) (4)

Clinical:

1. Pivotal Phase 3 Studies (1237.5/6)

The replicate, pivotal Phase 3 studies 1237.5 and 1237.6 are designed to satisfy both the US and EU regulatory requirements with regards to confirmatory evidence of the long term efficacy and safety of tiotropium + olodaterol FDC. The protocol for 1237.5 is provided in Appendix 12.5, while specific aspects of the trial design and analysis plan are discussed in Section 10.4.2.

No discussion occurred.

1a. Statistical Analysis Plan: hypothesis testing strategies for the primary endpoint

While the overall treatment duration in the pivotal studies will be 52 weeks to ensure sufficient exposure for an adequate assessment of the safety of tiotropium + olodaterol FDC, the primary efficacy analysis is specified after 24 weeks of treatment, in accordance with the EU regulatory requirements for medicinal products intended for the maintenance treatment of COPD.

Does the Agency have any comments regarding the primary efficacy analysis after 24 weeks of treatment?

Division Response:

The planned efficacy analysis at 24 weeks is acceptable. (See response to 1g for additional statistical comments.)

No discussion occurred.

A health-related quality-of-life instrument, the SGRQ, has been included as a pre-specified primary endpoint as a measure of symptomatic benefit, in accordance with EU requirements. As these trials are designed to satisfy both US and EU registration requirements, two hierarchical testing strategies are described in the trial statistical analysis plan. The testing strategy to support the US NDA will focus on the lung function endpoints (FEV₁ AUC₀₋₃ and trough FEV₁); however, all analyses, including the SGRQ total score, will be presented in the clinical trial reports.

Does the Agency agree with pre-specification of separate hypothesis testing strategies for US and EU?

Division Response:

Yes, we agree.

Discussion:

The sponsor asked the Division to characterize its policy regarding use of the SGRQ as an efficacy endpoint in COPD development programs. The Division stated that there is no general policy regarding the SGRQ and noted that its acceptability as a clinical endpoint has been questioned both within and outside the Agency. The Division acknowledged use of the SGRQ in prior COPD development programs, such as phosphodiesterase inhibitors, and in its use to support product registration in the EU.

(b) (4)

(b) (4)

Does the Agency agree with the identification of FEV₁ AUC₀₋₃ and trough FEV₁ as primary endpoints for the US hypothesis testing strategy?

Division Response:

The designated primary efficacy endpoints appear acceptable. A statistically significant treatment effect for each monocomponent will be expected for both FEV₁ AUC₀₋₃ and trough FEV₁ to support the proposed COPD indication

No discussion occurred.

Does the Agency agree that the US hypothesis testing strategy is adequate for the control of Type I error?

Division Response:

The proposed hierarchical hypothesis testing strategy appears adequate to control for Type I error.

No discussion occurred.

In accordance with accepted standards for the investigation of combination products, each combination dose is tested vs. the respective components: (i) tiotropium + olodaterol (5/5 µg) vs. tiotropium (5 µg) and olodaterol (5 µg); (ii) tiotropium + olodaterol (2.5/5 µg) vs. tiotropium (2.5 µg) and olodaterol (5 µg). The primary testing strategy does not include a test of tiotropium + olodaterol (2.5/5 µg) vs. tiotropium (5 µg). However, in the situation where tiotropium (5 µg) is finally registered in the US, as a second step, tiotropium + olodaterol (2.5/5 µg) FDC will be tested versus tiotropium (5 µg).

Does the Agency agree?

Division Response:

The proposed testing strategy appears sufficient to assess the individual contribution of each monocomponent to the tiotropium/olodaterol combination product. In addition, if more than one dose level is proposed in the NDA submission, you will be expected to demonstrate the benefit of the higher fixed dose combination over the lower fixed dose combination.

No discussion occurred.

1b. Exclusion of Placebo Arm

The trial design for 1237.5/6 includes two doses of tiotropium + olodaterol FDC (2.5/5 µg, 5/5 µg). In addition, the respective monotherapy arms (tiotropium (2.5 µg), tiotropium (5 µg), olodaterol (5 µg)) are included in order to confirm that the efficacy (FEV₁) of tiotropium + olodaterol FDC is statistically superior to the tiotropium and olodaterol mono-products. The studies have been designed without a placebo arm, for the reason outlined in Section 10.4.2.1. Three other studies within the Phase 3 program will include a placebo arm and will provide an opportunity to compare tiotropium + olodaterol FDC, as well as tiotropium and olodaterol mono compounds vs. placebo (1237.20, 1237.13, 1237.14; 6 weeks treatment duration for all three studies).

In response to a question in the pre-IND briefing package in December 2007, the FDA commented that a trial design that does not include a placebo may be acceptable.

Since the primary objective of the pivotal Phase 3 clinical trials is to compare the efficacy and safety of tiotropium + olodaterol FDC versus the individual components (tiotropium, olodaterol), does the Agency agree that the inclusion of a placebo arm in studies 1237.5/6 is not necessary?

Division Response:

Yes, we agree that a placebo arm is unnecessary, noting that the efficacy and safety of the combination product will rely on the efficacy and safety demonstrated for the tiotropium and olodaterol monotherapies. See the Introductory Comment.

No discussion occurred.

1c. Description of 24 hour FEV₁-time profile



Division Response:

No, we do not agree. We recommend characterizing the 24-hour FEV₁-time profiles in a subset of patients from the pivotal trials, 1237.5 and 1237.6.

Discussion:



^{(b) (4)} data from the pivotal pulmonary function trials (1237.5/6) characterizing the full 24-hour FEV₁-time curve will be needed for labeling. The Division recommends assessing serial spirometry for 24 hours following a single inhaled dose. The Division suggested that the sponsor review other related product labels for further guidance. The Division added the caveat that the Arcapta (indacaterol) product label may not be an ideal reference given the complexity of that specific clinical program.

1d. Inclusion / Exclusion Criteria

The inclusion and exclusion criteria for the Phase 3 program for tiotropium + olodaterol FDC are consistent with the criteria specified in the Phase 3 programs for tiotropium and olodaterol mono-products.

Does the Agency agree with the inclusion and exclusion criteria specified in 1237.5/6?

Division Response:

The trial participation criteria for 1237.5/6 appear acceptable.

No discussion occurred.

Ie. Adequacy of extent of exposure

(b) (4)

Division Response:

No, we do not agree. We expect that the results of the ongoing large safety trial (205.452) comparing tiotropium delivered via Handihaler versus Respimat will be available at the time of NDA submission. See the Introductory Comment.

No discussion occurred.

If. Safety PD assessment

The dose-response and PK/PD relationship of potassium was thoroughly characterized in Phase 1 and Phase 2 for olodaterol monoproduct and tiotropium + olodaterol FDC. In addition, in the olodaterol Phase 3 studies (1222.11-14), potassium levels were measured at 1 and 3 hours post-dose, in order to investigate the relationship with dose and plasma concentrations as recommended by the Agency (EoP 2 meeting for olodaterol mono-product).

BI therefore believes that effects of olodaterol on potassium have been adequately profiled and that there is no need to include specific potassium measurements (other than safety laboratory testing) in the Phase 3 studies for tiotropium + olodaterol FDC.

Does the Agency agree?

Division Response:

The proposed assessment of the tiotropium/olodaterol combination product on potassium levels is acceptable.

No discussion occurred.

Ig. General Comments

Does the Agency have any additional comments regarding the trial design for 1237.5/6?

Division Response:

- 1. We recommend that you conduct an adjudicated safety analysis of death, strokes, and cardiovascular adverse events, as well as respiratory-related deaths, intubations, and hospitalizations related to COPD, asthma, or pneumonia. We refer you to similar analyses conducted for other LAMA and LABA development programs.*
- 2. You propose to apply a restricted maximum likelihood (REML)-based repeated measures analysis with a spatial covariance structure to evaluate treatment differences in the primary efficacy endpoints, FEV₁ AUC_{0-3h} and trough FEV₁. In the protocol, justify the use of this covariance structure and/or consider an asymptotically consistent (sandwich) estimator. Outline additional analyses to gauge the sensitivity of your primary analysis method to the chosen covariance structure.*

Discussion:

The sponsor stated that their preference is to reflect the outcome of their discussion in the TSAP, rather than the protocol and asked if this was acceptable. The sponsor also asked whether the Division had a preference regarding the covariance structure and whether this preference extended across therapeutic areas/Divisions. The Division agreed that it is appropriate to describe these analyses in the TSAP rather than the protocol and further stated that the choice of the covariance structure for the primary efficacy analysis was theirs but they should include justification for that choice in the TSAP as well as provide sensitivity analysis to examine the robustness of the conclusions to the assumed covariance structure. The Division added that these comments apply for this application only and are not applicable to other Divisions.

- 3. You note that missing data for subjects who discontinue the trial due to “worsening” will be imputed with a worst-observation-carried-forward approach. In addition, you indicate that all other cases of missing data will not be imputed and will be handled by the repeated measures analysis. In the protocol, clarify whether “worsening” refers to deterioration in FEV₁, for example, or does it also refer to unacceptable side effects or safety (e.g., dropouts due to adverse event). Dropout from adverse events could be treatment-related; therefore, it may be difficult to justify the missing at random assumption for these subjects. Also, in the protocol, describe the anticipated impact the single imputation may have on the repeated measures analysis in that a variance of zero is being assumed for these subjects from the point of dropout onward. Include estimates for the proportion of subjects expected to be imputed using this worst-observation-carried-forward approach. Outline additional analyses to gauge the sensitivity of your primary analysis method to these issues surrounding the missing data approach.*

Discussion:

The sponsor asked if the Division had any guidance regarding the methods used for missing data. The Division stated that we are not in a position to endorse a specific approach to the missing data for the primary efficacy analysis but suggested that the sponsor consider the expected proportion of drop outs and the reasons for the drop outs in finalizing their plans for addressing

missing data. After prompting from the sponsor, the Division further indicated that reflecting these decisions in the TSAP rather than the protocol was acceptable.

In response to the SGRQ discussion resulting from question 1a, the Division further commented that if the sponsor anticipates making a claim in labelling regarding SGRQ, the Division would expect the protocol to include plans for control of type I error, incorporating this endpoint, as well as plans describing the approach for missing data for this endpoint.

2. Dose selection strategy

The rationale for the doses of tiotropium + olodaterol FDC selected for the Phase 3 program is described in Section 10.3.3.6.

Does the Agency have any comments regarding the dose selection strategy of tiotropium + olodaterol FDC?

Division Response:

We are unable to confirm the proposed olodaterol 5 mcg dose based on the limited summary information provided in the briefing materials. In addition, if two dose levels of the combination product are proposed for registration, you will be expected to demonstrate the benefit of the higher dose over the lower dose. See the Introductory Comment and the response to Question 1b.

No discussion occurred.

3. Posology of tiotropium + olodaterol FDC

Based on the rationale described in Section 10.3.3.6, BI does not intend to conduct any specific dosing frequency studies for tiotropium + olodaterol FDC.

While BI recognises that the FDA is currently not in a position to comment on the viability of the once daily posology for either tiotropium RESPIMAT or olodaterol, does the Agency agree that in general, the posology of a combination product will follow the posology of the mono-products, and as such formal dosing frequency studies for the combination are not necessary?

Division Response:

In principle, we agree that the dosing regimen of the combination product will correspond with the dosing frequency established for each monocomponent.

No discussion occurred.

4. Potential chemical/physical interaction of tiotropium + olodaterol

Reference is made to the clinical comment from the FDA at the pre-IND meeting in December 2007 regarding the investigation of a potential physical/chemical interaction of tiotropium and

olodaterol. BI has investigated the chemical and physical interaction of the ingredients. These studies included Spray content uniformity (SCU) and particle size distribution measurements by laser diffraction (LD) as well as by Andersen cascade impactor (ACI) for the combination product as well as for the mono products tiotropium and olodaterol.

As a result no chemical or physical interaction in the inhalation solution of the FDC including no change in performance parameter SCU could be detected. Comparing particle size distributions determined by LD of all batches, no relevant difference in performance could be seen. This observation was independently confirmed by the particle size distributions measured with the ACI for tiotropium and olodaterol. Based on these results, BI concludes that there are no relevant physical/chemical interactions of tiotropium and olodaterol. This is supported by the absence of any relevant PK interactions between tiotropium and olodaterol in Study 1237.3.

A summary of the results and respective figures can be found in Appendix 12.12.

Does the FDA agree that from a clinical perspective, based on the presented assessment no relevant physical/chemical interactions of tiotropium and olodaterol are present within the FDC?

Division Response:

Yes, we agree.

No discussion occurred.

5. Acceptability of Phase 3 program to support registration

(b) (4)

Division Response:

No, we do not agree. We expect that results of the large tiotropium safety trial will be available as supportive safety information at the time of NDA submission for the tiotropium/olodaterol combination product. See the Introductory Comment and the response to Question 1e.

Also, we have the following comments regarding evaluation of the device component in the Phase 3 program:

- Assess dose counter performance.*
- Perform in vitro testing (e.g., spray content uniformity, droplet size distribution etc.) of a small number (e.g., 100) of devices that are apparently functioning normally in subjects' hands near the end of the life of the device to ensure ruggedness throughout the*

product's intended span of use. Such an assessment is to evaluate the use of the device in the patient's hands from a device handling/mishandling perspective.

- *Evaluate all devices that are reported to be defective or malfunctioning during the clinical trials to the extent possible, and provide a report in the NDA as to their cause. Take appropriate corrective actions as necessary to minimize the risk of such failures in the commercial product and describe them in the NDA.*

Post meeting note: BI's responses, dated August 2, 2011, regarding the above comments related to the evaluation of the device component in the Phase 3 program are acceptable.

No discussion occurred.

Clinical Pharmacokinetics/Pharmacodynamics

6. *PK characterization of tiotropium + olodaterol FDC*

BI has conducted PK sampling for tiotropium + olodaterol (5/5 µg) FDC in the Phase 2 Study 1237.4 in patients with COPD. BI intends to further characterize the PK of tiotropium + olodaterol (5/5 µg) FDC and also tiotropium + olodaterol (2.5/5 µg) FDC in patients with COPD in the Phase 3 Study 1237.20 as described in the draft study protocol (provided in Appendix 12.6).

Does the Agency agree that studies 1237.4 and 1237.20 will adequately characterize the PK of tiotropium + olodaterol FDC?

Division Response:

We agree

No discussion occurred.

Does the Agency have any comments on the planned PK sampling scheme and data analysis in 1237.20?

Division Response:

We agree with your planned PK sampling scheme and proposed data analysis in protocol 1237.20. Provide estimates of relative systemic exposure (ratio with 90% CI) from FDC relative to olodaterol alone and tiotropium alone arms. As with any other application, we may request additional analysis based on the review of the submitted data at the time of NDA review.

Discussion: The sponsor wanted to clarify that this PK sampling scheme is for exploratory reasons and not to assess bioequivalence. The Division acknowledged and noted that the study is not powered to show bioequivalence. However, we would like to see the data in the requested format.

7. *Results of PK interaction study (1237.3)*

Reference is made to the discussions with the Agency at the pre-IND meeting. BI has now completed the PK interaction study (1237.3) comparing the PK of tiotropium + olodaterol (5/10 µg) FDC with the PK of the mono-products. Based on the results described in Section 10.3.2.3 and 10.5.1, BI has concluded that there is no meaningful PK interaction between the two compounds when administered as a fixed dose combination. Thus, as agreed at the pre-IND meeting, BI plans to use PK results from tiotropium and olodaterol mono-products to support the PK characterization of tiotropium + olodaterol FDC with respect to features such as PK in special populations, drug-drug interactions, etc..

Does the Agency agree that Study 1237.3 provides sufficient confirmation that there is no relevant PK interaction between tiotropium and olodaterol?

Division Response:

Based on your briefing package, we note that systemic exposure from FDC Respimat is higher (11-12%) compared to olodaterol Respimat alone, which may indicate PK interaction. Without reviewing individual data and the completed study report, it is difficult to draw definitive conclusions about PK interaction. The assessment of clinical significance of this higher exposure is ultimately a NDA review issue.

No discussion occurred.

BI requests confirmation from the Agency that the studies that have been / will be performed (listed in Table 10.5: 1) are sufficient, and that no further PK studies with tiotropium + olodaterol FDC are required.

Division Response:

We agree that studies listed in Table 10.5:1 with supporting data from PK trials for monoproducts listed in Table 10.5:2 will be sufficient for NDA filing.

No discussion occurred.

8. *QT study*

For olodaterol mono-product, a thorough QT study (1222.8) was conducted and accepted by the FDA as sufficient (i.e. no multiple-dose QT study was necessary). For tiotropium mono-product, a thorough QT study (205.302) was also conducted and accepted by the FDA as sufficient.

In light of these two studies and given that the exposure levels of olodaterol and tiotropium within the fixed dose combination are covered by the exposure studied in the mono-product QT studies, BI believes that a specific thorough QT study for the tiotropium + olodaterol FDC is not necessary.

Does the FDA agree?

Division Response:

We agree that a specific thorough QT study for the tiotropium + olodaterol FDC is not necessary. Again, we reiterate our previous recommendation that you collect ECGs in your Phase 3 program and submit ECG data with your NDA.

Discussion:

The sponsor clarified that 12-lead ECG data from the Phase 3 clinical program planned for submission in the combination product NDA will be generated at 8 time points from approximately 5000 patients, thus totaling 40,000 ECGs. In addition, Holter monitoring data will be available for approximately 650 patients over two 24-hour measurement periods each. The sponsor asked whether this volume of ECG data is acceptable. The Division stated that this proposal was acceptable.

Nonclinical

9. Adequacy of Olodaterol mono nonclinical program

The proposed nonclinical safety program for tiotropium + olodaterol FDC was included in the pre-IND meeting package. The official FDA minutes of this meeting included the following statement: "Our previous comments for the olodaterol/tiotropium FDC development plan were made based on the assumption that an adequate nonclinical program for the olodaterol mono-product is completed. For completion of the olodaterol mono-product nonclinical program, we expect the following studies: Conduct a valid in vivo micronucleus assay using olodaterol mono-product alone at an acceptable limit dose as previously communicated under IND 76,362. Complete the chronic repeat dose inhalation toxicology studies in the rat and dog and the reproductive toxicology battery (male and female fertility and pre- and post-natal development studies) for olodaterol mono-product. Review of these studies will determine the need for additional studies." BI has now completed all requested olodaterol nonclinical studies.

BI requests Agency confirmation that the present nonclinical safety program for olodaterol, including the above mentioned nonclinical safety studies, will be adequate to support the NDA for tiotropium + olodaterol FDC.

Division Response:

Pending the review of all study reports, it appears that the nonclinical development program that has been discussed with the Agency will be sufficient.

No discussion occurred.

10. Adequacy of tiotropium + olodaterol FDC nonclinical program

The nonclinical safety program for tiotropium + olodaterol FDC is described in Section 11 and includes the pharmacological, pharmacokinetic and toxicological studies (up to 13-week

combination studies in the dog at 3 different dose ratios) on the combination of tiotropium + olodaterol.

Does the Agency agree that the nonclinical safety program for the combination of tiotropium + olodaterol, including the pharmacokinetic drug-drug interaction studies will be adequate to support the NDA for tiotropium + olodaterol FDC?

Division Response:

Yes, we agree that the nonclinical safety program for the combination of tiotropium + olodaterol is adequate to support the NDA for tiotropium + olodaterol FDC, provided that the nonclinical safety program of the olodaterol monoproduct is adequate.

Additional Nonclinical Comment:

Provide structures of impurities and intermediates of the drug substance and drug product. Monitor impurities and degradation products of all active ingredients. Refer to the ICH Guidance for qualification of drug impurities in drug substances [ICH Q3A(R)] and degradants in drug products [ICH Q3B(R)]. If applicable, conduct the appropriate toxicity studies to qualify impurities and degradants. Impurities or intermediates that are identified as structural alerts should be at or below acceptable qualification thresholds for genotoxic and carcinogenic impurities as described in the draft FDA Guidance for Industry, Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches (December 2008) for assessment of impurities to support clinical studies for the IND and NDA.

No discussion occurred.

Administrative

11. **BI currently plans to submit the NDA for tiotropium + olodaterol FDC**

(b) (4)

(b) (4)

Division Response:

See the Introductory Comment.

See discussion under the Introductory Comment

3.0 ISSUES REQUIRING FURTHER DISCUSSION
N/A

4.0 ACTION ITEMS
N/A

5.0 ATTACHMENTS AND HANDOUTS
N/A

IND 76397

Page 17

Initialed by:

BPorter/22JUL2011

SLimb/25JUL2011

PRoy/21JUL2011

RDavi/27JUL2011

JBuenconsejo/1AUG2011

SSeymour/25JUL2011

BChowdhury/4AUG2011

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/s/

EUNICE H CHUNG-DAVIES
08/04/2011



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF NEW DRUG QUALITY ASSESSMENT

Sponsor Name:	Boehringer Ingelheim Pharmaceuticals, Inc.
Application Number:	IND 76,397
Product Name:	Tiotropium + Olodaterol Respimat® Inhalation Spray
Meeting Type:	Type B
Meeting Category:	End-Of-Phase 2 -CMC
Meeting Date and Time:	August 3, 2011 , 1:30-2:30 pm (EST)
Meeting Location:	Teleconference
Received Briefing Package	June 17, 2011

The following consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled as a Teleconference on August 3, 2011, 1:30-2:30 pm (EST) between Boehringer Ingelheim Pharmaceuticals, Inc and the Center for Drug Evaluation and Research/Office of New Drug Quality Assessment. This material is shared to promote a collaborative and successful discussion at the meeting. The minutes of the meeting will reflect agreements, key issues, and any action items discussed during the formal meeting and may not be identical to these preliminary comments. If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of canceling the meeting (contact Swati Patwardhan, Regulatory Health Project Manager for Quality, (301) 796-4085). It is important to remember that some meetings, particularly milestone meetings, are valuable even if the pre-meeting communications are considered sufficient to answer the questions. **Please note that if there are any major changes to the questions (based on our responses herein), we may not be prepared to discuss or reach agreement on such changes at the meeting.** If any modifications to the development plan or additional questions for which you would like FDA feedback arise prior to the meeting, contact the Regulatory Project Manager for Quality to discuss the possibility of including these for discussion at the meeting.

1.0 Background

BI 1744 / Tiotropium Respimat® Inhalation Spray is being developed to treat Long-term, once daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. The purpose of the meeting is to discuss the status of BI's CMC development program and to obtain the Agency's feedback on specific CMC topics.

2.0 Pre-meeting Responses

2.1 Characterization of Drug Product

Drug Product Characterization Studies (DPCS) according to the recommendations in the FDA's Guidance for Industry on "Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation, July 2002", that are solely related to the performance of Respimat® inhaler have already been performed with various Respimat® inhalation spray products (i.e., Spiriva®, Combivent®, BI 1744 Respimat® Inhalation Spray). BI proposes that these Characterization Studies solely related to the performance of the Respimat® inhaler will not be repeated with BI 1744 / tiotropium Respimat® Inhalation Spray. Only those DPCS will be performed that are specifically impacted by the inhalation solution. These studies will be performed using the most sensitive concentration(s) of the drug product for the study being performed.

The approach summarized in Table 6 is consistent with the approach followed for BI 1744 Respimat® Inhalation Spray and reflects recommendations received from FDA at the BI 1744 Respimat® EOP2 meeting.

Does FDA agree with the drug product characterization studies proposed to be performed and the concentrations to be used for the individual studies?

FDA Pre-meeting Response: *Your proposed approaches and concentrations appear acceptable as long as there haven't been any changes in the device since the other Respimat products were studied. You should include in the NDA to be submitted, appropriate justifications and clear reference to the supporting data in already submitted application(s) so that a logical and acceptable link is built for the Agency to conduct pertinent evaluations.*

2.2 Control Strategy for Drug Product

The proposed list of tests includes the "universal tests" as required in the ICH Q6A Guideline. Specific tests relevant to this dosage form as identified in FDA's "Guidance for Industry: Nasal Spray and Inhalation Solution, Suspension and

Spray Drug Products” (July 2002)” are also included. Additionally, sterility testing is included in compliance with 21 CFR 200.51, Aqueous-based drug products for oral inhalation.

Does FDA agree to the proposed test parameters for control of the drug product and BI’s justification of test procedures and specifications for the proposed testing parameters?

FDA Pre-meeting Response:

1. *Your proposed test parameters appear acceptable for control of the drug product.*
2. *Your justification of test procedures and specifications for the proposed testing parameters also appear acceptable; however, note that the determination of drug product specifications is a review issue at the NDA stage.*
3. *Your approach in testing the clinical return samples in Phase 3 trials, based on already acquired device performance data, is acceptable.*
4. *Your control strategy for leachables is acceptable provided that materials of construction for the device to be used in the current product remain the same as those of the previously reviewed ^{(b) (4)} model of the Respimat device.*

2.3 Primary stability studies and in-use stability studies for the drug product

The proposed shelf-life of the drug product will be based on the primary stability data from three batches of the intended commercial dosage strength of BI 1744 / tiotropium Respimat[®], Inhalation Spray.

The in-use stability investigations are proposed to be carried out (over the shelf life of the drug product) on one of the two formulated strengths to be tested in Phase 3 clinical trials, but not the other. This proposal is based on the premise that in-use stability from one of the below dosage strengths will be fully representative of the other, and therefore sufficient to support registration of either strength.

- 2.5 µg BI 1744 / 2.5 µg tiotropium Respimat Inhalation Spray (per actuation)
- 2.5 µg BI 1744 / 1.25 µg tiotropium Respimat Inhalation Spray (per actuation)

Does FDA agree with the proposed design of the primary stability and in-use stability study for the drug product?

FDA Pre-meeting Response:

1. *Your proposed design of the primary stability study for the drug product is acceptable.*
2. *Your proposed design of the in-use stability study for the drug product is also acceptable, however, you are recommended to conduct the study on the product with the lowest strength. You should also provide a summary of the*

supporting data in the NDA to demonstrate that the stability behavior of Spiriva® Respimat® with respect to the degradation of tiotropium and performance parameters is independent of the concentration of tiotropium in an appropriate concentration range that brackets the concentration of the tested product.

2.4 Proposed Waiver from Stability Study on Respimat® Inhaler with 28 actuations

For physician samples to be introduced to the patients, BI intends to use a Respimat® Inhaler that delivers 28 actuations rather than 60 actuations as planned for the commercial product.

The only difference between the physician samples and the commercial product will be the locking mechanism of the Respimat® inhaler; all other aspects are identical in the two presentations.

As a result, BI proposes to conduct (in addition to the primary stability studies conducted according to ICH Q1A(R2) on the 60 actuation inhaler), one-time studies with the physician samples to prove that the 28 actuation inhaler provides the same quality as the 60 actuation inhaler.

FDA's September 25, 2008 feedback to this same proposal previously communicated by BI in association with the CMC EOP2 Meeting for the BI 1744 CL Respimat® mono product (IND 76-362) agreed in principle to the described one-time physician sample studies, but recommended that BI also provide 6 months accelerated stability data at 40°C / 75% RH, in order to demonstrate that the storage conditions do not deleteriously impact the performance of the locking mechanism.

Does FDA agree with BI's proposal to only perform the described one-time studies without an additional stability study for the 28 actuation inhaler?

FDA Pre-meeting Response: *Your proposal is acceptable for the purpose of NDA review. The post approval studies for the 28 actuation inhaler should be handled in the same way as the 60 actuation commercial product.*

3.0 Concurrency:

{See appended electronic signature page}

Swati Patwardhan.
Regulatory Health Project Manager for Quality, Division III
Office of New Drug Quality Assessment

{See appended electronic signature page}

Prasad Peri, Ph.D.
Branch Chief, Branch VIII, Division III
Office of New Drug Quality Assessment

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/s/

SWATI A PATWARDHAN
07/29/2011

ALAN C SCHROEDER
07/29/2011
signed for Prasad Peri, Ph.D.

LATE-CYCLE COMMUNICATION
DOCUMENTS



NDA 206756

LATE-CYCLE MEETING MINUTES

Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

Attention: Anna Wysowskyj, MBA
Senior Associate Director, Regulatory Affairs

Dear Ms. Wysowskyj:

Please refer to your New Drug Application (NDA) dated and received May 22, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Stiolto Respimat (tiotropium bromide and olodaterol) Inhalation Spray.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on February 24, 2015.

A copy of the official minutes of the LCM is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Christine Ford, Regulatory Project Manager, at (301) 796-3420.

Sincerely,

{See appended electronic signature page}

Anthony Durmowicz, M.D.
Cross-Discipline Team Leader
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: February 24, 2015 at 9:00 A.M.
Meeting Location: Teleconference

Application Number: NDA 206756
Product Name: Stiolto Respimat (tiotropium bromide/olodaterol) Inhalation Spray
Applicant Name: Boehringer Ingelheim Pharmaceuticals, Inc. (BI)

Meeting Chair: Dr. Anthony Durmowicz, Cross-Discipline Team Leader
Meeting Recorder: Christine Ford, Regulatory Project Manager

FDA ATTENDEES:

Anthony Durmowicz, MD, Cross-discipline Team Leader, DPARP
Robert Lim, MD, Clinical Reviewer, DPARP
Christine Ford, RPh, Regulatory Project Manager, DPARP
Eugenia Nashed, PhD, Product Quality Reviewer, Office of New Drug Products (ONDP)
Craig Bertha, PhD, CMC Lead, ONDP
Linda Ng, PhD, Senior Policy Advisor, Office of Process and Facilities
Lan Zeng, PhD, Biometrics Reviewer, Division of Biometrics II
Dipti Kalra, RPh, Safety Evaluator, Division of Pharmacovigilance I
Felicia Duffy, RN, BSN, MEd, Division of Risk Management
Tamra Meyer, PhD, Epidemiologist, Division of Epidemiology I

EASTERN RESEARCH GROUP ATTENDEES:

(b) (6), Eastern Research Group, Inc.
(b) (6) Eastern Research Group, Inc.

APPLICANT ATTENDEES:

Disse, Dr. Bernd	Head Corporate Medical Respiratory	Ingelheim
Tetzlaff, Dr. Kay	Medical	Ingelheim
Loaiza, Dr. Lazaro	Pharmacovigilance	Ingelheim
Bothner, Dr. Ulrich	Pharmacovigilance	Ingelheim
Wasmund, Annette	Global Regulatory	Ingelheim
Oellers, Dr. Nadja	Project Management	Ingelheim
Mauz, Dr. Annerosa	Nonclinical Safety	Bieberach
Kunz, Dr. Christina	Clinical Pharmacology	Bieberach
Dittgen, Dr. Tanjew	R&D Project Management	Bieberach
Hamilton, Dr. Alan	Medical	BI Canada
McBryan, Dr. Danny	Medical	BIPI Main Campus

Otulana, Dr. Tunde	Head US Medical	BIPI Corp. Center
Petit, Dr. Claude	Head US Data and Statistics	BIPI Corp. Center
Zhao, Dr. Mary	Statistics	BIPI Corp. Center
Korducki, Larry	Statistics	BIPI Corp. Center
Webb, Jim	Regulatory CMC	BIPI Corp. Center
King, Dr. Josephine	Regulatory Labeling	BIPI Corp. Center
Billingham, Kelly	Regulatory Promotion	BIPI Corp. Center
Snyder, Jeff	Regulatory	BIPI Corp. Center
Wysowskyj, Anna	Regulatory	BIPI Corp. Center

BACKGROUND:

NDA 206756 was submitted on May 22, 2014, for Stiolto Respimat (tiotropium bromide/olodaterol) Inhalation Spray.

Proposed indication(s): Chronic obstructive pulmonary disease (COPD)

PDUFA goal date: May 22, 2015

FDA issued a Background Package in preparation for this meeting on February 10, 2015.

LCM AGENDA:

1. Introductory Comments (RPM/CDTL)

Welcome, Introductions, Objectives of the meeting

2. Review Issues

Two manufacturing facilities, one domestic and one international, have yet to be inspected.

Discussion:

FDA stated that the manufacturing facilities have been inspected. Final evaluation is on going.

3. Information Requests

Response to the October 29, 2014, information request was received November 26, 2014. There are no further information requests at this time.

4. Major labeling issues

There are no major labeling issues at this time. An FDA edited label will be sent to BI within 1-2 weeks after the LCM.

5. Review Plans

The objectives for the remainder of the review cycle are to complete all reviews and finalize labeling.

6. Wrap-up and Action Items

Internal Wrap-up meeting scheduled for March 31, 2015.

Complete manufacturing facility inspections.

PDUFA goal date is May 22, 2015.

Additional discussion:

BI asked whether FDA can provide guidance regarding the submission minor revisions to the clinical trial reports (CTRs) for phase 3 studies 1237.5, 1237.6, and 1237.9991, as requested in an email dated January 27, 2015.

FDA responded that they have looked at the revisions and agree that the revisions do not appear to affect data interpretation or conclusions. The Division has also contacted the FDA electronic submissions group regarding how to submit the revisions, but has not received a response yet. The Division suggested that BI can also contact FDA electronic submissions.

In response to the applicant's inquiry whether FDA expects to take an early action on this NDA, FDA stated that that determination has not yet been made and will depend on remaining action items.

This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

Post-meeting addendum:

In an email correspondence dated March 18, 2015, Valerie Gooding, Regulatory Information Specialist with FDA/CDER/Division of Data Management Services and Solutions (DDMSS), provided the requested information to Anna Wysowskyj, Director of Regulatory Affairs at BI.

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/s/

ANTHONY G DURMOWICZ
03/26/2015



NDA 206756

**LATE CYCLE MEETING
BACKGROUND PACKAGE**

Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

Attention: Anna Wysowskyj, MBA
Senior Associate Director, Regulatory Affairs

Dear Ms. Wysowskyj:

Please refer to your New Drug Application (NDA) dated and received May 22, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Stiolto Respimat (tiotropium bromide and olodaterol) Inhalation Spray.

We also refer to the Late-Cycle Meeting (LCM) scheduled for February 24, 2015. Attached is our background package, including our agenda, for this meeting.

If you have any questions, call Christine Ford, Regulatory Project Manager, at (301) 796-3420.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: February 24, 2015 at 9:00 A.M.
Meeting Location: Teleconference – Provide call in number and Passcode

Application Number: NDA 206756
Product Name: Stiolto Respimat (tiotropium bromide/olodaterol) Inhalation Spray
Indication: Chronic obstructive pulmonary disease (COPD)
Sponsor/Applicant Name: Boehringer Ingelheim Pharmaceuticals, Inc. (BI)

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

1. Discipline Review Letters

No Discipline Review letters have been issued to date.

2. Substantive Review Issues

No substantive review issues have been identified to date.

ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned.

REMS OR OTHER RISK MANAGEMENT ACTIONS

No issues related to risk management have been identified to date.

LCM AGENDA:

1. Introductory Comments (RPM/CDTL)

Welcome, Introductions, Objectives of the meeting

2. Discussion of Review Issues

Two manufacturing facilities, one domestic and one international, have yet to be inspected.

3. Information Requests

Response to the October 29, 2014, information request was received November 26, 2014.
There are no further information requests at this time.

4. Major labeling issues

There are no major labeling issues at this time. An FDA edited label will be sent to BI within 1-2 weeks after the LCM.

5. Review Plans

The objectives for the remainder of the review cycle are to complete all reviews and finalize labeling.

6. Wrap-up and Action Items

Internal Wrap-up meeting scheduled for March 31, 2015.

Complete manufacturing facility inspections.

PDUFA goal date is May 22, 2015.

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/s/

BADRUL A CHOWDHURY
02/10/2015