

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207070Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 207070/Original 1

SUPPL #

HFD # 570

Trade Name Spiriva Respimat

Generic Name tiotropium bromide

Applicant Name Boehringer Ingelheim

Approval Date, If Known 9/15/15

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.

N/A

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:

N/A

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

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# 21936 Spiriva Respimat for COPD

NDA# 21395 Spiriva HandiHaler

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#

NDA#

NDA#

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:

Trials 205.416, 205.417, 205.418, 205.419, 205.442, 205.444, 205.456, and 205.464

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.")

All investigations listed under 2(c) YES NO
(Trials 205.416, 205.417, 205.418, 205.419, 205.442, 205.444, 205.456, and 205.464)

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?

All investigations listed under 2(c) YES NO
(Trials 205.416, 205.417, 205.418, 205.419, 205.442, 205.444, 205.456, and 205.464)

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"):

Trials 205.416, 205.417, 205.418, 205.419, 205.442, 205.444, 205.456, 205.464

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?

All investigations/trials listed under 2(c) and 3(c)

IND # 65127 YES ! NO
! Explain:

Investigation #2
IND # 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: Jessica K. Lee, PharmD
Title: Senior Regulatory Project Manager
Date: 9/15/15

Name of Office/Division Director signing form: Badrul A. Chowdhury, MD, PhD
Title: Director

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/

JESSICA K LEE
09/15/2015

BADRUL A CHOWDHURY
09/15/2015

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 207070/Original 1 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: Spiriva Respimat Established/Proper Name: tiotropium bromide Dosage Form: inhalation spray		Applicant: Boehringer Ingelheim Agent for Applicant (if applicable):
RPM: Jessica Lee		Division: DPARP
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)		For ALL 505(b)(2) applications, two months prior to EVERY action: <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>) Date of check:
<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>9/15/15</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. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

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

- | | |
|---|---|
| <input type="checkbox"/> Fast Track | <input type="checkbox"/> Rx-to-OTC full switch |
| <input type="checkbox"/> Rolling Review | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input type="checkbox"/> 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

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

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- 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 (approvals only)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input type="checkbox"/> Yes <input checked="" 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 (approvals only)	<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 (including approval letter with final labeling)	Action(s) and date(s) AP 9/15/15
Labeling	
❖ Package Insert (write submission/communication date at upper right of first page of PI)	
• Most recent draft labeling (if it is division-proposed labeling, it should be in track-changes format)	<input checked="" type="checkbox"/> Included
• Original applicant-proposed labeling	<input checked="" type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (write submission/communication date at upper right of first page of each piece)	<input 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 (if it is division-proposed labeling, it should be in track-changes format)	<input checked="" type="checkbox"/> Included
• Original applicant-proposed labeling	<input checked="" type="checkbox"/> Included
❖ Labels (full color carton and immediate-container labels) (write submission/communication date on upper right of first page of each submission)	
• Most-recent draft labeling	<input checked="" type="checkbox"/> Included
❖ Proprietary Name	Acceptable 8/18/15; 12/5/14 Acceptable 8/10/15; 12/4/14
• Acceptability/non-acceptability letter(s) (indicate date(s))	
• Review(s) (indicate date(s))	
❖ Labeling reviews (indicate dates of reviews)	RPM: <input type="checkbox"/> None 10/20/14 DMEPA: <input type="checkbox"/> None 9/10/15; 2/6/15 DMPP/PLT (DRISK): <input type="checkbox"/> None 6/25/15; 6/23/15 OPDP: <input type="checkbox"/> None 8/20/15 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Other: <input type="checkbox"/> None
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting (indicate date of each review)	10/20/14
❖ 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 (signed by Division Director)	<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
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>5/27/15</u> If PeRC review not necessary, explain: _____ 	
<ul style="list-style-type: none"> ❖ 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>) 	8/28/15; 8/25/15; 8/7/15; 8/5/15; 7/10/15; 6/25/15 (2); 5/20/15; 4/24/15; 3/2/15; 2/24/15; 1/7/15; 1/6/15; 10/24/14; 10/16/14; 10/15/14; 8/27/14
<ul style="list-style-type: none"> ❖ 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) 	
<ul style="list-style-type: 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>) • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) • EOP2 meeting (<i>indicate date of mtg</i>) • Mid-cycle Communication (<i>indicate date of mtg</i>) • Late-cycle Meeting (<i>indicate date of mtg</i>) • Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>) 	<input checked="" type="checkbox"/> N/A or no mtg <input type="checkbox"/> No mtg 12/9/13 <input type="checkbox"/> No mtg 6/9/08 <input checked="" type="checkbox"/> N/A <input checked="" type="checkbox"/> N/A N/A
<ul style="list-style-type: none"> ❖ Advisory Committee Meeting(s) <ul style="list-style-type: none"> • Date(s) of Meeting(s) 	<input checked="" type="checkbox"/> No AC meeting
Decisional and Summary Memos	
<ul style="list-style-type: none"> ❖ 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 9/11/15
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 9/14/15
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None 9/1/15 (2)
Clinical	
<ul style="list-style-type: none"> ❖ Clinical Reviews <ul style="list-style-type: none"> • Clinical Team Leader Review(s) (<i>indicate date for each review</i>) • Clinical review(s) (<i>indicate date for each review</i>) • Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	<input type="checkbox"/> No separate review 9/4/15; 5/21/15; 10/14/14 <input type="checkbox"/> None
<ul style="list-style-type: 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>) 	Clinical review 5/21/15, page 15.
<ul style="list-style-type: none"> ❖ 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 6/23/15
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input type="checkbox"/> None requested 5/20/15; 4/6/15; 3/31/15
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 type="checkbox"/> No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 9/15/15; 6/10/15; 10/15/14
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 6/8/15; 9/29/14
❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	<input type="checkbox"/> None requested
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None 5/22/15; 10/10/14
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	<input type="checkbox"/> None requested

Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> No separate review
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None 6/9/15; 10/16/14
❖ Microbiology Reviews <input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	CMC review dated 6/9/15, Page 59
<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"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within 2 years of action date) <i>(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁵)</i>	Date completed: 6/9/15; 11/24/14 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within 30 days of action date) <i>(original and supplemental BLAs)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

⁵ i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Day of Approval Activities

❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • 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>)
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<input type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input 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 type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input type="checkbox"/> Done

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

/s/

JESSICA K LEE
09/15/2015



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

ELECTRONIC CORRESPONDENCE

DATE: August 28, 2015

To: Amy Van Andel, DVM, MPH Director, Regulatory Affairs	From: Jessica Lee, PharmD Sr. Regulatory Project Manager
Company: Boehringer Ingelheim	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: NA	Fax number: 301-796-9728
Phone number: 203-791-5452	Phone number: 301-796-3769

Subject: NDA 207070; Spiriva Respimat Labeling Information Request

**Total no. of pages including
cover:**

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Dear Dr. Van Andel,

We refer to NDA 207070 for SPIRIVA[®] RESPIMAT[®] (tiotropium bromide) inhalation spray and to your proposed revised labeling submitted on August 21, 2015. Please find enclosed our revisions to your proposed package insert (PI). The enclosed PI is a follow-up to our comments sent on August 25, 2015, with minor edits and clarifications. Be advised that additional labeling changes may be forthcoming as the labeling review continues. We will use the new version of the label that you submit to make further changes.

Submit a clean copy and a tracked-change version of the label incorporating the revisions in the attached package insert to the NDA by Close of Business, Monday, August 31, 2015. In addition, please forward a courtesy copy via email to Jessica.Lee@fda.hhs.gov. If you have any questions, please contact Jessica Lee, Sr. Regulatory Project Manager, at 301-796-3769.

NDA 207070

Drafted by: JLee 8/28/15

Initialed by: ADurmowicz 8/28/15
SNabavian for LJafari 8/28/15

Finalized by: JLee 8/28/15

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

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/s/

JESSICA K LEE
08/28/2015



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

ELECTRONIC CORRESPONDENCE

DATE: August 25, 2015

To: Amy Van Andel, DVM, MPH Director, Regulatory Affairs	From: Jessica Lee, PharmD Regulatory Project Manager
Company: Boehringer Ingelheim	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number:	Fax number: 301-796-9728
Phone number: 203-791-5452	Phone number: 301-796-3769

Subject: NDA 207070 Spiriva Respimat Information Request/Comment

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Dear Dr. Van Andel,

We refer to NDA 207070 for SPIRIVA® RESPIMAT® (tiotropium bromide) inhalation spray and to your proposed revised labeling submitted on August 21, 2015.

We have the following comments regarding your proposed revisions to the label. Note that these comments reiterate our position on these specific sections of the label, and do not serve as negotiating points. Furthermore, these comments are not all-inclusive, and we will have additional changes to the label which will be forthcoming.

Section 1: Indications and Usage

- As mentioned in our labeling IR dated August 8, 2015, our intent is to avoid unnecessary limitations of use in the indication. The primary role of the INDICATIONS AND USAGE section of labeling is to clearly and concisely communicate the drug's approved indication. Based on 21CFR 201.56 and 21CFR 201.57, this section must only contain a summary of the essential scientific information needed for the safe and effective use of the drug. Information regarding the clinical trial population and background medications is provided in Section 14. Note that even for LABAs for which there is a safety concern for use without baseline anti-inflammatory therapy, recent indication statements (see BREO ELLIPTA) do not include background therapies used by the clinical trial population and unlike LABAs, there is no information to date to indicate that Spiriva Respimat use in the absence of ICS background therapy represents a safety risk. For consistency, the WARNINGS AND PRECAUTION section stating that Spiriva Respimat as (b) (4) can be deleted.

Section 14.2: Asthma

- Your counterproposal regarding information about the (b) (4) dose is unacceptable. As stated in previous interactions, we believe that it is important to inform prescribers that there was a (b) (4)
- Based on the data you provided in the NDA, it is apparent that the time to full bronchodilator effect may be greater than (b) (4), and thus our original proposed language should be retained.

NDA 207070

Drafted by: SChin 8/25/15
JLee 8/25/15

Initialed by: ADurmowicz 8/25/15
LJafari 8/25/15

Finalized by: JLee 8/25/15

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/s/

JESSICA K LEE
08/25/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 207070

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

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

ATTENTION: Amy Van Anandel, DVM, MPH
Director, Regulatory Affairs

Dear Dr. Anandel:

Please refer to your New Drug Application (NDA) dated and received August 15, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tiotropium Bromide Inhalation Spray, 1.25 mcg per Actuation.

We also refer to your correspondence dated and received July 8, 2015, requesting review of your proposed proprietary name, Spiriva Respimat.

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

If any of the proposed product characteristics as stated in your July 8, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

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 Jessica Lee, Regulatory Project Manager in the Office of New Drugs, at (301) 796-3769.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
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
08/18/2015



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

ELECTRONIC CORRESPONDENCE

Date: August 7, 2015

To: Amy E. Van Andel, DVM, MPH Director, Regulatory Affairs	From: Christine Ford, R.Ph. Regulatory Project Manager
Company: Boehringer Ingelheim Pharmaceuticals, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: 203-798-5452	Fax number: 301-796-9728
email: amy.vanandel@boehringer-ingelheim.com	Phone number: 301-796-3420

Subject: NDA 207070 Spiriva Respimat (tiotropium) inhalation spray
FDA labeling comments

Total no. of pages including cover: 24

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

Submit response by close of business Friday, August 21, 2015

Document to be mailed: YES NO

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We refer to NDA 207070 for Spiriva Respimat and to your proposed revised labeling submitted on July 23, 2015. Attached are our revisions to your proposed Spiriva Respimat labeling. In addition, we have provided in the comments below, the rationale for some of our proposed revisions. Our comments and recommendations are not all-inclusive, nor final, and additional comments may be forthcoming as the labeling review continues.

Section 1: Indications and Usage

- We eliminated the phrases “add-on” and “who remain symptomatic on at least inhaled corticosteroids” in order to broaden the indication. You have demonstrated efficacy over a broad range of asthma severities and your proposed indication unnecessarily limits Spiriva Respimat to patients who have failed ICS.
- A Limitation of Use has been added to both the COPD and asthma indications. This inclusion is consistent with labeling of other maintenance therapies indicated to improve lung function.

Section 6.2: Clinical Trials Experience in Asthma

- We ask that you revise Table 2 and the lists of adverse reactions below the table in 1% to 2% and <1% of patients to include all adverse events that occur more in patients who receive Spiriva Respimat 2.5 mcg compared to placebo. For less common adverse reactions, limit to events with an incidence $\geq 0.5\%$. While we note your pharmacovigilance methods by which you attempt to ascertain whether an adverse event (any untoward event) should be classified as an adverse reaction (some evidence of drug causality), the longstanding method used by DPARP in labeling to define an adverse reaction is an adverse event that occurs in greater frequency than that found in patients who receive placebo. Your use of pharmacovigilance endpoints rather than preferred terms is acceptable as long as all of the preferred terms are captured within the PV endpoints. This was the case with the adverse reactions listed in Table 1 for the COPD program, however, there appear to be adverse reactions (those occurring in Spiriva Respimat 2.5 mcg > placebo) in your asthma program that are not captured by the PV endpoints.

Section 14.2: Asthma

- We have included mention of the dose-ranging trial in the severe asthma population (study 341) in the Dose Selection subheading as well as mention that a dose response relationship was not clearly established in the dose selection studies.
- We have included trials 416 and 417 as Trials 4 and 5 in the description of clinical trials and the demographics table. As part of your clinical program, these trials cannot be completely removed from the label, but at the same time efficacy findings are not relevant to the 2.5 mcg dose. Therefore, these trials are only mentioned briefly as listed above.
- We acknowledge your decision to remove all information regarding (b) (4). However, we have inserted language into the text to describe (b) (4).

(b) (4) in order better inform health care providers of the rationale for selection of the 2.5 mcg dose so they can make an informed decision when determining the risk-benefit of the 2.5 mcg (b) (4) dose for their patients.

- Note that we have included corresponding exacerbation rate data in Table 7. We view the a reduction in the rate of exacerbations as a better determination of efficacy than time to first exacerbation which is more of a determination of risk and, as such, is more appropriate as a safety study endpoint (or as an exacerbation endpoint when patients who have an exacerbation are removed from a study). Tiotropium 5 mcg data for rate and time to first exacerbation is also included as text below the table.
- We have inserted data regarding the ACQ results from Trials 418 and 419. For balance, AQLQ responses have also been included.
- We substantially shortened the section on adolescent trials 444 and 456 because efficacy in this age group is largely extrapolated from that in adults.

Send your responses via secure email to jessica.lee@fda.hhs.gov no later than August 21, 2015. Your response will subsequently need to be submitted officially to the NDA. If you have any questions, please contact Jessica Lee @ 301-796-3769.

Drafted by: SChin, ADurmowicz/ 8.7.2015
cford/ 8.7.2015

Initialed by: LJafari/ 8.7.2015

Finalized: cford/ 8.7.2015

20 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
08/07/2015



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

ELECTRONIC CORRESPONDENCE

DATE: August 5, 2015

To: Amy Van Andel, DVM, MPH Director, Regulatory Affairs	From: Jessica Lee, PharmD Senior Regulatory Project Manager
Company: Boehringer Ingelheim	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number:	Fax number: 301-796-9728
Phone number: 203-798-5452	Phone number: 301-796-3769

Subject:

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Dear Dr. Van Andel:

We have considered your comments dated July 2, 2015, regarding the deferred pediatric study(ies) necessary to fulfill the Pediatric Research and Equity and Act. You will be required to conduct the following trials:

- A 48-week, randomized, double-blind, parallel-group, placebo-controlled, efficacy and safety study of tiotropium delivered via the Respimat device in children 6-11 years of age with moderate asthma. The study should evaluate at least 2 doses of tiotropium and include approximately 125 patients per treatment arm.

Study Completion Date MM/YY
Final Report Submission Date MM/YY

- A 12-week, randomized, double-blind, parallel-group, placebo-controlled, efficacy and safety study of tiotropium delivered via the Respimat device in children 6-11 years of age with severe asthma. The study should evaluate at least 2 doses of tiotropium and include approximately 125 patients per treatment arm.

Study Completion Date MM/YY
Final Report Submission Date MM/YY

Provide your agreement and/or revisions along with proposed timelines for completion by August 14, 2015.

If you have any questions, please contact Jessica Lee, Regulatory Project Manager, at 301-796-3769.

NDA 207070

Drafted by: ADurmowicz 8/4/15
JLee 8/4/15

Initialed by: ADurmowicz 8/4/15
LJafari 8/4/15

Finalized by: JLee 8/5/15

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/s/

JESSICA K LEE
08/05/2015



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

ELECTRONIC CORRESPONDENCE

DATE: July 10, 2015

To: Amy Van Andel, DVM, MPH Director, Regulatory Affairs	From: Jessica Lee, PharmD Regulatory Project Manager
Company: Boehringer Ingelheim	Division of Pulmonary and Allergy Drug Products
Fax number:	Fax number: 301-796-9728
Phone number: 203-798-5452	Phone number: 301-796-2300
Subject: NDA 207070 Spiriva Respimat Information Request	

Total no. of pages including cover:

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Dear Dr. Van Andel:

Your submission dated August 15, 2014, to NDA 207070, is currently under review. As we continue our review of your proposed product label, we would like to better understand the effects of Spiriva Respimat on the AQLQ and ACQ. We ask that you make your response to this request a priority as we cannot move forward with labeling discussions without this information. Please submit the following:

1. Populate the table below with information from trials 205.416, 205.417, 205.418, 205.419, 205.422, 205.444, and 205.456. Consider patients with an improvement of 0.5 units as a responder for each endpoint. Note that you will need to add additional rows to accommodate data from all trials and that all treatment arms should be included.
2. Provide tipping point sensitivity analyses to evaluate the impact of missing data. These analyses should vary assumptions about average values of the relevant endpoint among the patients on each Spiriva Respimat and placebo arms who withdrew from the trial early. Include the possibility that patients with missing data from the Spiriva Respimat arms had worse outcomes than patients with missing data from the placebo arm. Ensure that documentation submitted with your report defines the distributions used to generate values for withdrawn patients and explains how those distributions were obtained.
3. Provide the datasets and programs for all analyses. The analysis datasets should include a column or columns which clearly indicate whether each observation was missing, observed while the patient was on randomized treatment, or observed after the patient discontinued randomized treatment.

	Trial XXX			Trial XXX			Trial XXX		
	Tio R5	Tio R 2.5	Placebo	Tio R5	Tio R2.5	Placebo	Tio R5	Tio R2.5	Placebo
AQLQ									
N									
Baseline									
Change from baseline									
Mean difference from placebo (95% CI, p-value)									
Responder rate* (n [% improvement]) (95% CI, p-value)									
ACQ7									
N									

Baseline									
Change from baseline									
Mean difference from placebo (95% CI, p-value)									
Responder rate (n [% improvement]) (95% CI, p-value)									
ACQ5									
N									
Baseline									
Change from baseline									
Mean difference from placebo (95% CI, p-value)									
Responder rate (n [% improvement]) (95% CI, p-value)									

*Define AQLQ responders as those with a difference in score of ≥ 0.5 for overall quality of life

Submit the information by close of business, Tuesday, July 14, 2015. The information can be sent by electronic mail to Jessica.Lee@fda.hhs.gov, followed by an official submission to the NDA. If you have any questions, please contact Jessica Lee, Regulatory Project Manager, at 301-796-3769.

NDA 207070
Spiriva Respimat

Drafted by: SCHin/ 7.9.15
JLee/7.10.15

Initialed by: LJafari/7.10.15
SCHin/ADurmowicz/7.10.15
DPetullo7.10.15

Finalized by: JLee/7.10.15

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/s/

JESSICA K LEE
07/10/2015



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Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

DATE: June 25, 2015

To: Amy Van Andel, DVM, MPH Director, Regulatory Affairs	From: Jessica Lee, PharmD Regulatory Project Manager
Company: Boehringer Ingelheim	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number:	Fax number: 301-796-9728
Phone number: 203-798-5452	Phone number: 301-796-3769
Subject: NDA 207070 Labeling	

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Dear Dr. Van Andel:

Your submission dated August 15, 2014, to NDA 207070, is currently under review. Reference is also made to the labeling submission dated May 15, 2015. We have the following comments:

After review of your most recent proposed labeling, we note that substantial revision is necessary to the package insert prior to being able to conduct a more granular line by line review. We have outlined some of the necessary revisions with respect to content and organization of the label below, primarily for Sections 6 and 14. Use the outline provided to revise the product label as we have described. The outline provided is for the body of the package insert, but corresponding changes should also be carried to the Highlights section and Table of Contents.

Section 6. Adverse Reactions

6.2: Clinical Trials Experience in Asthma

- Table 2
 - Provide the source for adverse reactions included; it appears as if adverse reactions which should be listed, e.g., bronchitis, headache, oropharyngeal discomfort/pain, are missing
 - Clarify which “similar terms” were grouped.
- Other reactions at an incidence between 1% and 2%
 - Clarify how adverse reactions were determined for this list. It appears that hypertension, allergic rhinitis/conjunctivitis, abdominal pain, diarrhea, and pyrexia should be included.
- Less Common Adverse Reactions
 - Again, clarify how adverse reactions were selected for this heading.

Section 14. Clinical Studies

14.2: Asthma

- Subsection: Dose-Ranging and Dose-Regimen Studies
 - After description of the five dose-ranging/dose regimen trials, descriptively state that the ^{(b) (4)}
- Subsection: Confirmatory Studies
 - General comments:
 - Rename trials as Trial 1, Trial 2, etc. with Studies 416 and 417 designated as Trials 4 and 5.
 - Separate the adolescent studies from the adult studies; descriptions and results from adolescent studies should follow all adult studies

- Table 5: Re-organize according to the attached template labeled “Baseline Characteristics”
 - Following the table, (b) (4)
[Redacted]
 - Table 6: Re-organize according to the attached template labeled “Peak and trough FEV1”
 - Note that replicate studies should not be pooled
 - [Redacted] (b) (4)
 - [Redacted] (b) (4)
 - Figure 2: Peak and trough FEV1 response over 24 weeks
 - Remove [Redacted] (b) (4)
 - Remove [Redacted] (b) (4)
 - State that [Redacted] (b) (4)
 - Exacerbations:
 - Table 7: Replace [Redacted] (b) (4)
 - (b) (4) Remove [Redacted] (b) (4)
 - [Redacted] (b) (4)
- [Redacted] (b) (4)

Baseline Characteristics

	Adults, 18 yrs and older				
	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5
Demographics					
Mean age in years (range)					(b) (4)
Mean duration of asthma (years)					
(b) (4) smoked (%)					
Laboratory					
Absolute eosinophils, median ($10^9/L$)					
Total IgE, median (microgram/L)					
Pulmonary function test					
Predose FEV1 (L) (b) (4)					(b) (4)
% Reversibility					
Absolute reversibility (mL)					
FEV1/FVC (b) (4) post-bronchodilator					



In addition, attached are our revisions to your proposed package insert (PI). Be advised that these labeling changes are not the Agency's final recommendations and that additional labeling changes will be forthcoming as the labeling review continues. We will use the new version of the label that you submit to make further changes. We ask that you provide a reasonable timeline in which you will be able to submit the revised version of the label so that we may resume our review of the label.

Submit a clean copy and a tracked-change version of the label incorporating the recommendations noted above and in the attached package insert to the NDA. In addition, please forward a courtesy copy to Jessica Lee via email.

If you have any questions, please contact Jessica Lee, Regulatory Project Manager, at 301-796-3769.

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/s/

JESSICA K LEE
06/25/2015



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 Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

DATE: June 24, 2015

To: Amy Van Andel, DVM, MPH Director, Regulatory Affairs	From: Jessica Lee, PharmD Regulatory Project Manager
Company: Boehringer Ingelheim	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number:	Fax number: 301-796-9728
Phone number: 203-798-5452	Phone number: 301-796-3769

Subject: NDA 207070 PREA IR

Total no. of pages including cover:

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Dear Dr. Van Andel:

Your submission dated August 15, 2014, to NDA 207070, is currently under review. We have the following comment and request for information:

Given the change in the proposed dose of Spiriva Respimat for asthma, your proposed pediatric program evaluating [REDACTED] (b) (4) 2.5 mcg/day will not be sufficient. Therefore, to fulfill the Pediatric Research Equity Act, you will need to conduct the following trial and provide the requested milestone timeline:

A [REDACTED] (b) (4) week, randomized, double-blind, parallel-group, placebo-controlled, efficacy and safety study in children 6-11 years of age with asthma. [REDACTED] (b) (4)

Final Protocol Submission Date: MM/YY
Study Completion Date: MM/YY
Final Report Submission Date: MM/YY

Provide your agreement and/or revisions along with proposed timelines for completion by July 2, 2015.

If you have any questions, please contact Jessica Lee, Regulatory Project Manager, at 301-796-3769.

Drafted by: SChin 6/23/15
JLee 6/23/15

Initialed by: LJafari 6/23/15
CHill 6-24-15
SSeymour 6/24/15

Finalized by : JLee 6/25/15

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JESSICA K LEE
06/25/2015



NDA 207070

**REVIEW EXTENSION –
MAJOR AMENDMENT**

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

Attention: Amy Van Andel, DVM, MPH
Director Regulatory Affairs

Dear Dr. Van Andel:

Please refer to your New Drug Application (NDA) dated August 15, 2014, received August 15, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Spiriva Respimat.

On April 30, and May 8 and 15, 2015, we received your April 30, and May 8 and 15, 2015, submissions that constitute major amendments to this application. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is September 15, 2015.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with “PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2013 THROUGH 2017.” If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by August 18, 2015.

If you have any questions, call Jessica Lee, Regulatory Project Manager, at (301) 796-3769.

Sincerely,

{See appended electronic signature page}

Ladan Jafari
Chief, Project Management Staff

Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

LADAN JAFARI
05/20/2015



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ELECTRONIC CORRESPONDENCE

DATE: April 24, 2015

To: Amy Van Andel, DVM, MPH Director, Regulatory Affairs	From: Jessica Lee, PharmD Regulatory Project Manager
Company: Boehringer Ingelheim	Division of Pulmonary and Allergy Drug Products
Fax number:	Fax number: 301-796-9728
Phone number: 203-798-5452	Phone number: 301-796-2300

Subject:

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Comments:

Document to be mailed: YES xNO

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Dear Dr. Van Andel:

Your submission dated August 15, 2014, to NDA 207070, is currently under review. Also, refer to the teleconference with the Agency on April 20, 2015. We have the following requests for information. If these data were previously submitted, provide the submission date.

1. Briefly summarize what is the same between the 1.25 mcg and 2.5 mcg products, e.g., manufacturing, components, device, etc. Specify any changes implemented to either product since the approval of NDA 21936.
2. List (b) (4) supporting data, i.e., either submit the data as Appendix or provide detailed references to prior submissions.

Address the following items:

- a. Formulations, including different ratio of API to other components
 - b. Stability data supporting proposed expiry for 1.25 mcg product
 - c. In-use stability period and supporting data for 1.25 mcg product
 - d. (b) (4)
3. Provide current Specifications and Stability Protocol for the 1.25 mcg product and specify any differences from the prior versions.
 4. Submit revised container closure labeling to clearly distinguish between the 1.25 mcg and 2.5 mcg products.
 5. Briefly summarize differences between the total dose of medication received by the patient when administered as 2 actuations (puffs) of 1.25 mcg product *versus* 1 actuation of 2.5 mcg product.

Submit the information by close of business, Thursday, April 30, 2015. The information can be sent by electronic mail to Jessica.Lee@fda.hhs.gov, followed by an official submission to the NDA. If you have any questions, please contact Jessica Lee, Regulatory Project Manager, at 301-796-3769.

Drafted by: ENashed/ 4.23.15
JLee/4.23.15

Initialed by: LJafari/4.23.15
CBertha/4.23.15
SChin/4.23.15
ADurmowicz/4.23.15
ENashed/4.23.15
JPinto/4.23.15

Finalized by: JLee/4.24.15

Drafted by: ENashed 4.23.15
JLee 4.23.15

Initialed by: LJafari
CBertha
JPinto

Finalized by:

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/s/

JESSICA K LEE
04/24/2015



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

ELECTRONIC CORRESPONDENCE

DATE: March 2, 2015

To: Amy Van Andel, DVM, MPH Director, Regulatory Affairs	From: Jessica Lee, PharmD Regulatory Project Manager
Company: Boehringer Ingelheim	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number:	Fax number: 301-796-9728
Phone number: 203-791-5452	Phone number: 301-796-3769

Subject: NDA 207070 Spiriva Respimat Information Request

**Total no. of pages including
cover:**

Comments: Please confirm receipt.

Document to be mailed: YES xNO

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Dear Dr. Van Andel,

Your NDA, 207070 dated August 15, 2014, is currently under review. We have the following requests for information:

1. We are not able to replicate the results from your interim analysis for the primary endpoint time to first severe exacerbation using pooled data from studies 205.416 and 205.417. The dataset EXACI from the pooled studies contains time to first severe exacerbation from period -1 (screening period) not period 1 (treatment period). Submit the interim dataset that contains interim data from period 1 with a detailed description of the interim analysis including the interim data lock meeting minutes.
2. Submit the independent Data Monitoring Committee (IDMC) charter and all meeting minutes including any from closed sessions.

Submit the information by Monday, March 9, 2015. The information can be sent by electronic mail to Jessica.Lee@fda.hhs.gov, followed by an official submission to the NDA. If you have any questions, please contact Jessica Lee, Regulatory Project Manager, at 301-796-3769.

NDA 207070

Drafted by: KHamilton/2.27.15
JLee/2.27.15

Initialed by: LJafari/2.27.15
DPetullo/3.1.15

Finalized by: JLee/3.2.15

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/s/

JESSICA K LEE
03/02/2015



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

ELECTRONIC CORRESPONDENCE

DATE: February 24, 2015

To: Amy Van Andel, DVM, MPH Director, Regulatory Affairs	From: Jessica Lee, PharmD Regulatory Project Manager
Company: Boehringer Ingelheim	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number:	Fax number: 301-796-9728
Phone number: 203-791-5452	Phone number: 301-796-3769

Subject: NDA 207070 Spiriva Respimat Information Request

**Total no. of pages including
cover:**

Comments: Please confirm receipt.

Document to be mailed: YES xNO

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Dear Dr. Van Andel,

Your NDA, 207070 dated August 15, 2014, is currently under review. On January 20, 2015, you submitted FEV1-time profile following the first dose treatment of tiotropium from study 205.380. In addition to this information, we request you submit additional analyses (tables and figures):

1. The FEV1 peak_{0-3h} and FEV1 AUC_{0-3h} response analysis, following the first dose of tiotropium, similar to Table 11.4.1.1:1 and Table 11.4.1.1:2 in 0205-0380-01-15-study report body.pdf
2. A sub-group analysis of FEV1 peak_{0-3h}, FEV1 AUC_{0-3h} response and FEV1 time-profile, following the first dose of tiotropium, stratified by the patients' concomitant medicine background (i.e., patients with or without β 2-adrenoceptor agonists treatment between visit 1 and visit 2). The output files would be:
 - a. Descriptive summary of baseline comparison of PFTs in patients with or without β 2-adrenoceptor agonists treatment.
 - b. Patients with β 2-adrenoceptor agonists treatment. Tables of FEV1 peak_{0-3h} and FEV1 AUC_{0-3h} response comparing different doses of tiotropium with placebo similar to Table 11.4.1.1:1 and Table 11.4.1.1:2. Figure of FEV1-time profile similar to Figure 11.4.1.2.1:1
 - c. Patients without β 2-adrenoceptor agonists treatment. Tables of FEV1 peak_{0-3h} and FEV1 AUC_{0-3h} response comparing different doses of tiotropium with placebo similar to Table 11.4.1.1:1 and Table 11.4.1.1:2. Figure of FEV1-time profile similar to Figure 11.4.1.2.1:1
 - d. Three figures of FEV1-time profile with each figure comparing one dose of tiotropium with placebo. Each figure should contain 4 curves: placebo with β 2-adrenoceptor agonists, placebo without β 2-adrenoceptor agonists, tiotropium with β 2-adrenoceptor agonists, and tiotropium without β 2-adrenoceptor agonists.

Submit the information by Monday, March 2, 2015. The information can be sent by electronic mail to Jessica.Lee@fda.hhs.gov, followed by an official submission to the NDA. If you have any questions, please contact Jessica Lee, Regulatory Project Manager, at 301-796-3769.

NDA 207070

Drafted by: YRen/2.24.15
JLee/2.24.15

Initialed by: SBrar/2.24.15
LJafari/2.24.15

Finalized by: JLee/2.24.15

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/s/

JESSICA K LEE
02/24/2015



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

ELECTRONIC CORRESPONDENCE

DATE: January 7, 2015

To: Amy Van Andel, DVM, MPH Director, Regulatory Affairs	From: Jessica Lee, PharmD Regulatory Project Manager
Company: Boehringer Ingelheim	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number:	Fax number: 301-796-9728
Phone number: 203-791-5452	Phone number: 301-796-3769

Subject: NDA 207070 Spiriva Respimat Information Request

Total no. of pages including cover:

Comments: Please confirm receipt.

Document to be mailed: YES xNO

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Dear Dr. Van Andel,

Your NDA, 207070 dated August 15, 2014, is currently under review. We have the following requests for information:

1. According to Table 9.5.8:1 on page 63 of 0205-0380-01-15-study report body.pdf, PFT was performed 10 minutes prior to and up to 3 hours after trial drug administration at Visit 2. Provide the data and figure similar to Figure 11.4.1.2.1:1 on page 96 to describe the FEV1-time response profile following the first dose of tiotropium inhalation.
2. A discrepancy is noted with the reported PK parameter estimates between the values in the reported text and the tables. Provide written justification reconciling the table values and the values in the reported statements.
 - a. On page 159 of 0205-0416-01-15-study report body.pdf, you mentioned “*Dosing to steady-state resulted in 1.45-fold higher C_{max} values as compared with single dose administration of Tio R5. Similarly, total exposure based on $AUC_{0-0.5}$ values was 1.62-fold higher at steady-state as compared with the administration of a single dose (Table 11.5.2:1). The 24 h urinary excretion of unchanged tiotropium (Ae_{0-24}) was 2.25-fold higher at steady state compared to the single dose.*” However, the reported values differ from the values estimated from Table 11.5.2:1 on page 157 in the same report.
 - b. On page 161 of 0205-0417-01-15-study report body.pdf, you mentioned “*Dosing to steady-state resulted in 1.23-fold higher C_{max} values as compared with single dose administration of Tio R5. Similarly, total exposure based on $AUC_{0-0.5}$ values was 1.69-fold higher at steady-state as compared with the administration of a single dose (Table 11.5.2: 1). The 24 h urinary excretion of unchanged tiotropium (Ae_{0-24}) was 1.46-fold higher at steady state compared to the single dose.*” However, the reported values differ from the values estimated from Table 11.5.2:1 on page 159 in the same report.

Submit the information by Wednesday, January 21, 2015. The information can be sent by electronic mail to Jessica.Lee@fda.hhs.gov, followed by an official submission to the NDA. If you have any questions, please contact Jessica Lee, Regulatory Project Manager, at 301-796-3769.

NDA 207070

Drafted by: YRen/1.7.15
JLee/1.7.15

Initialed by: LJafari/1.7.15
SBrar/1.7.15

Finalized by: JLee/1.7.15

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/s/

JESSICA K LEE
01/07/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 207070

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

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

ATTENTION: Amy Van Andel, DVM, MPH
Director, Regulatory Affairs

Dear Dr. Van Andel:

Please refer to your New Drug Application (NDA) dated August 15, 2014, received August 15, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tiotropium Bromide Inhalation Spray, (b) (4) per actuation.

We also refer to your September 12, 2014, correspondence, received September 12, 2014, requesting review of your proposed proprietary name, Spiriva Respimat.

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

If any of the proposed product characteristics as stated in your September 12, 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 Jessica Lee, Regulatory Project Manager in the Office of New Drugs, at (301) 796-3769.

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/

NICHELE E RASHID
12/05/2014

TODD D BRIDGES on behalf of KELLIE A TAYLOR
12/05/2014



NDA 207070

**FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED**

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

Attention: Amy Van Andel, DVM, MPH
Director Regulatory Affairs

Dear Dr. Van Andel:

Please refer to your New Drug Application (NDA) dated August 15, 2014, received August 15, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Spiriva Respimat.

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**.

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 May 18, 2015.

During our filing review of your application, we identified the following potential review issues:

Clinical:

We have concerns regarding the data in your NDA submission to support the proposed indication for Spiriva Respimat as a “long-term, once-daily, add-on maintenance treatment of asthma in patients 12 years of age and older who remain symptomatic on at least ICS”. We have the following review issues:

1. We note that the original intended indication for tiotropium HandiHaler developed under IND 046-687 was as a “^{(b) (4)} maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease, including chronic bronchitis, emphysema, ^{(b) (4)}

[Redacted]

2. You do not appear to have fully justified the proposed dose/dosing regimen for tiotropium Respimat in patients with asthma. ^{(b) (4)}

[Redacted]

[Redacted]

3. The peak_(0-3 hr) FEV₁ and trough FEV₁ response to tiotropium Respimat in even mild asthma patients not using concomitant LABA was only ^{(b) (4)} respectively. Thus, we question the utility of tiotropium Respimat as a bronchodilator in patients with asthma.

4. We question whether the patients enrolled in your clinical trials 205.416 and 205.417 actually had asthma. This is not a new issue regarding your asthma program and was previously conveyed to you during the June 9, 2008, End-of-Phase 2 meeting and the August 25, 2009, Type C meeting. Asthma is generally characterized by reversible airflow obstruction defined as demonstration of reversibility of FEV₁ to albuterol/salbutamol of at least 12% and 200 mL. However, in the above mentioned pivotal Phase 3 trials, not only was a determination of reversibility not required, but instead, the patients enrolled were required to demonstrate some degree of fixed airway obstruction (FEV₁ ≤ 80% predicted and FEV₁/FVC of ≤ 0.7) after administration of albuterol/salbutamol, thus meeting the primary diagnostic criteria for COPD. While some patients with severe asthma may not be fully reversible, you do not seem to have distinguished this relatively rare population from patients with COPD. The fact that the mean patient age in Trials 205.416 and 205.417 is significantly older than in your other asthma studies further suggests that these study patients may have had COPD rather than asthma. This limitation of your study design has been noted elsewhere in response to the publication of these study results in the NEJM (Huib A.M. Kerstjens, M.D., Michael Engel, M.D., et al., N Engl J Med 2012; 367:1198-1207 and Bel, E. Tiotropium for Asthma - Promise and Caution. N Engl J Med. Sep 27, 2012. 367;13: 1257-1259).
5. As mentioned previously at both at the June 9, 2008, End-of-Phase 2 meeting and the August 25, 2009, Type C meeting, we do not agree with the definition you used to determine asthma exacerbations. For example, the concept of an (b) (4) as an endpoint is unfounded. In addition, severe asthma exacerbations generally represent asthma-related hospitalizations, rather than a change in drug therapy such as a short burst of oral corticosteroid therapy as was used in your program.
6. Notwithstanding Comment #5, your proposed label includes an efficacy claim regarding the (b) (4). Note that a claim based on pooled data from your Phase 3 trials would be considered as one study whereas a claim for a (b) (4) would need to be supported by replicate data from at least two adequately designed clinical trials. This was previously conveyed to you at the June 9, 2008, End-of-Phase 2 meeting.
7. Note that the Asthma Control Questionnaire (ACQ) has not been accepted as a validated Patient Reported Outcome (PRO) for inclusion in drug product labels approved in the United States.
8. Given the issues noted above regarding study design, endpoints, and study populations, and given that tiotropium Respimat represents a new class of drug for the treatment of asthma, it is likely that the application will be the subject of an FDA advisory committee meeting.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded

upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

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.

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), and Information for Use (IFU). 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), and Instructions for Use (IFU), 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.

Pediatric studies conducted under the terms of section 505B of the Federal Food, Drug, and Cosmetic Act (the Act) may also qualify for pediatric exclusivity under the terms of section 505A of the Act. If you wish to qualify for pediatric exclusivity please consult Pulmonary, Allergy, and Rheumatology Products. Please note that satisfaction of the requirements in section 505B of the Act alone may not qualify you for pediatric exclusivity under 505A of the Act.

We acknowledge receipt of your request for a partial waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

We acknowledge receipt of your request for a partial deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial deferral request is denied.

If you have any questions, call Jessica Lee, Regulatory Project Manager, at (301) 796-3769.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, MD, PhD
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
10/24/2014



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

ELECTRONIC CORRESPONDENCE

DATE: October 16, 2014

To: Amy Van Andel, DVM, MPH Director, Regulatory Affairs	From: Jessica Lee, PharmD Regulatory Project Manager
Company: Boehringer Ingelheim	Division of Pulmonary and Allergy Drug Products
Fax number:	Fax number: 301-796-9728
Phone number: 203-798-5452	Phone number: 301-796-2300

Subject: NDA 207070 Spiriva Respimat-Information Request

Total no. of pages including cover:

Comments:

Document to be mailed: YES xNO

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Dear Dr. Van Andel:

Your NDA 207070 dated, August 15, 2014, is currently under review. We have the following request for information:

Provide additional information regarding Protocol 205.416 Site 49005 and Protocol 205.419 Germany Site 49057 (Olaf Schmidt, M.D.), Protocol 205.418 Washington Site 01019 (Stephen Tilles, MD), and Protocol 205.444 Chile Site 56001 (Carlos Quilodran, M.D.) in PDF electronic format. Please submit all the subject data listings, grouped by clinical study site and Protocol.

The study subject data listings should capture the following, as applicable:

1. Subject discontinuation (If applicable per treatment group: site subject number, screening visit date, randomization date (if applicable), informed consent date and/or assent date (if applicable), date of first dose/last dose, date of discontinuation, reason for discontinuation).
2. All reported adverse events (If applicable per treatment group: preferred term/investigator entry, date start/stopped, severity/resolution, Serious Adverse Event (yes/no), death (yes/no)).
3. Primary efficacy endpoint (site subject number, visit # and corresponding date (baseline, week 1...etc)).
4. Secondary efficacy endpoint (site subject number, visit # and corresponding date (baseline, week 1...etc)).
5. Protocol deviations or violations

Submit the information by Monday, October 20, 2014. The information can be sent by electronic mail to Jessica.Lee@fda.hhs.gov, followed by an official submission to the NDA. If you have any questions, please contact Jessica Lee, Regulatory Project Manager, at 301-796-3769.

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/s/

JESSICA K LEE
10/16/2014



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

ELECTRONIC CORRESPONDENCE

DATE: October 15, 2014

To: Amy Van Andel, DVM, MPH Director, Regulatory Affairs	From: Jessica Lee, PharmD Regulatory Project Manager
Company: Boehringer Ingelheim	Division of Pulmonary and Allergy Drug Products
Fax number:	Fax number: 301-796-9728
Phone number: 203-798-5452	Phone number: 301-796-2300

Subject: NDA 207070 Spiriva Respimat - Information Request 10/15/14

Total no. of pages including cover:

Comments:

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Your NDA, 207070 dated August 15, 2014, is currently under review. We have the following requests for information:

Clinical

1. Formally submit final clinical study reports and datasets for the four asthma clinical trials (205.121, 205.201, 205.202, and 205.203) conducted with the Spiriva Handihaler product to this NDA.
2. Submit absolute peak FEV₁ data for subjects in trials 205.418 and 205.419 or provide the location of this information in your NDA submission.
3. Provide data, if it exists, evaluating the use of Tiotropium Respimat in naive asthma patients (i.e., patients not on controller medications).

Clinical Pharmacology

4. The dosing regimen of tiotropium respimat for asthma does not appear to have been fully explored. To facilitate review of the dosing regimen information, supply the following information:
 - Based on the Type C Meeting correspondence (held on August 25, 2009), you agreed to characterize the once daily dose response relationship in your phase 2 trials. Provide a report characterizing the dose-response relationship within the dose range of 1.25 µg to 10 µg once daily administered in all phase 2 trials.
 - Provide reasoning why you did not observe dose response relationship in phase 3 trials (response is numerically better in 2.5 µg than 5 µg once daily treatment) while the opposite was observed in the phase 2 trials.
 - Provide a rationale why you did not include an additional lower dosing arm (such as 1.25 µg BID) in the dosing regimen trial 205.420. In the assessment of dosing posology during the Type C meeting held on August 25, 2009, your dose-selection (2.5 µg BID and 5 µg QD) for trial 205.420 was considered to be a non-traditional approach.

Submit the information by close of business, Tuesday, October 21, 2014. The information can be sent by electronic mail to Jessica.Lee@fda.hhs.gov, followed by an official submission to the NDA. If you have any questions, please contact Jessica Lee, Regulatory Project Manager, at 301-796-3769.

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/s/

JESSICA K LEE
10/15/2014



NDA 207070

NDA ACKNOWLEDGMENT

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

Attention: Amy Van Andel, DVM, MPH
Director Regulatory Affairs

Dear Dr. Van Andel:

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: Spiriva Respimat (tiotropium bromide) Inhalation Spray

Date of Application: August 15, 2014

Date of Receipt: August 15, 2014

Our Reference Number: NDA 207070

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 October 14, 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 Jessica Lee, Regulatory Project Manager, at (301) 796-796-3769.

Sincerely,

{See appended electronic signature page}

Jessica K. Lee, PharmD
Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

JESSICA K LEE
08/27/2014



IND 65127

MEETING PRELIMINARY COMMENTS

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

Attention: Amy Van Andel, DVM, MPH
Director, Drug Regulatory Affairs

Dear Dr. Van Andel:

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

We also refer to your September 20, 2013, correspondence, received September 20, 2013, requesting a meeting to discuss the proposed marketing application for the tiotropium Respimat asthma indication.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, call me at (301) 796-3769.

Sincerely,

{See appended electronic signature page}

Jessica K. Lee, PharmD
Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: December 9, 2013
Meeting Location: 1:00 PM – 2:30 PM (EST)

Application Number: IND 65127
Product Name: Spiriva Respimat (tiotropium bromide inhalation spray)
Indication: Asthma
Sponsor: Boehringer Ingelheim Pharmaceuticals, Inc.

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for December 9, 2013, 1:00 PM – 2:30 PM (EST) at FDA White Oak between Boehringer Ingelheim Pharmaceuticals, Inc. and the Division of Pulmonary, Allergy, and Rheumatology Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

Boehringer Ingelheim requested a Pre-NDA meeting in the correspondence dated September 20, 2013, to discuss the proposed marketing application for the tiotropium Respimat asthma indication. SPIRIVA RESPIMAT is indicated for the long term, once-daily, add-on maintenance treatment of asthma and in the prevention of bronchospasm, in patients 12 years of age and older who remain symptomatic on at least inhaled corticosteroids.

The meeting was granted on September 26, 2013. BI submitted the meeting package on November 7, 2013. BI's specific questions are provided in *italics* and the FDA responses are in normal font.

2.0 DISCUSSION

Question 1: *BI has assessed all issues in the Regulatory History section as being fully resolved. Does the FDA agree?*

Are there any other outstanding issues related to the interactions between BI and the FDA for tiotropium RESPIMAT that require resolution prior to the submission of the NDA?

FDA Response to Question 1:

We cannot agree at this time. Whether BI has addressed many of the issues discussed (dose selection/interval, patient population, etc.) will be a review issue.

Question 2: *Does the Division have any comments regarding the organization or pharmacokinetic approach proposed for Module 2.7.1 and 2.7.2?*

FDA Response to Question 2:

Your proposal seems reasonable. In addition, include the following aspects in your NDA:

- Clarify if the final to-be-marketed formulation was used in the 8 clinical studies for asthma where PK assessments were included. If not, outline how the formulations are bridged.
- In order to extrapolate clinical pharmacology information from previously approved NDA 21395 and previously submitted NDA 21936, the formulations used in the clinical pharmacology studies in those NDAs and the final to-be-marketed formulation for this NDA should be linked appropriately. In the NDA submission, clarify how the formulations are linked.
- New information for tiotropium may be available in published literature that was not available during the review of NDA 21395. You should conduct a literature survey and include any relevant new information in this NDA submission. The label may be updated as well if the information is relevant. For example, the following missing aspects related to clinical pharmacology may be addressed:
 - CYP induction potential of tiotropium
 - Tiotropium interaction with OCT2 or other efflux or uptake transporters included in the recently published draft DDI Guidance
 - Effect of hepatic impairment on tiotropium disposition
 - Any significant drug-drug interactions (case reports or human studies)

Question 3: *Does the Division agree with or have any comments on the internal and external factors that have been listed for comparisons in the mock summary of 2.7.2?*

FDA Response to Question 3:

You indicate that you will conduct sub-group analysis for efficacy (across different races as well as US population vs. populations from other countries). If PK data are available from these populations, include sub-group analysis for differences in systemic exposure of tiotropium based on these factors.

Question 4: *Assuming the pharmacokinetics of tiotropium following inhalation via RESPIMAT for adolescent patients with asthma is comparable to that for adults, does the Division agree with providing a summary of the pharmacokinetics for patients aged 12 years and older with asthma in the US PI vs. separate summaries for adult and adolescent patients?*

FDA Response to Question 4:

In general, a unified summary of the PK parameters in adults and adolescents will be included in the US PI. We reserve our detailed comments for this question at this stage as we have not reviewed the data.

Question 5: *Does the Division have any comments on the proposal for organization and analysis of the pivotal efficacy data?*

FDA Response to Question 5:

While pooled data from identical trials within different asthma severities is acceptable, note that the determination of efficacy for tiotropium Respimat in asthma will be based upon review of the results from individual studies. In particular, as previously communicated (End of Phase 2 meeting held June 9, 2008), (b) (4)

Question 6: *Does the Division agree with this approach to complying with the ISE requirements?*

FDA Response to Question 6:

Yes, the approach is reasonable.

Question 7: *Does the Division agree with the defined sub-populations? Does the Division have any suggestions regarding other sub-populations that should be considered?*

FDA Response to Question 7:

Your defined subpopulations are generally acceptable. Also include subgroup analyses based on eosinophil count and IgE level, and by bronchodilator reversibility at screening. In addition, to allow assessment of whether treatment effect differs across subgroups, provide analyses utilizing the relevant treatment-by-subgroup interaction term.

Question 8: *Does the Division have any other comments regarding the organization and/or proposed content in Module 2.7.3?*

FDA Response to Question 8:

No, we do not have any other comments.

Question 9: *Does the Division agree with this approach to complying with the ISS?*

FDA Response to Question 9:

While your overall proposal is reasonable, note that pooling across studies when treatment groups differ could be misleading. For example, comparison of Tio R 2.5 to placebo in the pooled analysis of studies 205.416, 205.417, and 205.456 may be misleading.

Question 10: *Does the Division agree with the defined sub-populations? Does the Division have any suggestions regarding other sub-populations that should be considered?*

FDA Response to Question 10:

We do not agree. Safety data should be pooled across all asthma severities and ages including Study 205.464 conducted in Japan. Subsequent subgroup analyses based on asthma severity and age should also be included.

Question 11: *Does the Division agree with this approach? Does the Division have any suggestions regarding other systems or syndromes that should be considered?*

FDA Response to Question 11:

Your approach is reasonable.

Question 12: *Does the Division have any other comments regarding the organization and/or proposed content in Module 2.7.4, including the approach to post-marketing data, adjudicated events or MedDRA classification?*

FDA Response to Question 12:

No, we do not have any other comments.

Question 13: *Does the Division agree to the proposal for Module 5.3.1.4?*

FDA Response to Question 13:

Your proposal seems reasonable.

Question 14: *Does the Division agree to the proposal for referencing the tiotropium HandiHaler and tiotropium RESPIMAT COPD clinical studies in the tiotropium RESPIMAT asthma sNDA?*

Does the Division agree that in the case of separate NDAs for the indications of COPD and asthma, BI can cross-reference COPD studies submitted to NDA 021936 in a NDA for SPIRIVA RESPIMAT in asthma? Would this cross-referencing be accepted in the case of separate NDAs for the indications of COPD and asthma, even if NDA 021936 were still under review at the time of the asthma NDA submission?

FDA Response to Question 14:

Your proposal to cross-reference is acceptable.

Question 15: *Based on the draft table of contents for Module 5 (Appendix 5) and the draft Tabular Listing of All Clinical Studies (Table 5.2) (Appendix 6), does the Division have any comments regarding the general organization and proposed content of Module 5?*

FDA Response to Question 15:

No, we do not have any comments.

Question 16: *Does the Division agree with the organization of Table 5.2(Appendix 6)?*

FDA Response to Question 16:

The organization of Table 5.2 is acceptable.

Question 17: *Does the Division agree with the approach for case narratives?*

FDA Response to Question 17:

Yes, we agree.

Question 18: *Does the Division have any comments on the proposal for the folder structure, CRFs, narratives, or clinical datasets to be submitted as described in Electronic submission proposal (Appendix 7)?*

FDA Response to Question 18:

No, we do not have any comments.

Question 19: *Does the Division agree with BI's proposal for the trials to include in the summary level clinical dataset?*

FDA Response to Question 19:

Your proposal is acceptable.

Question 20: *Does the Division agree that the application for patients with asthma aged 12 and older* (b) (4)

FDA Response to Question 20:

Yes, we agree.

Question 21: *Does the Division agree that a 120-day safety update report* (b) (4)

FDA Response to Question 21:

No, we do not agree. A 120 day safety update is required by regulation. However, if no relevant studies are ongoing or if data are blinded, the content may be limited.

Question 22: *Does the Division agree to the proposed approach to the nonclinical sections of Module 2; namely to include summary information on the two juveniles toxicology studies only?*

FDA Response to Question 22:

Yes, we agree.

Question 23: *Does the Division have any comments regarding the proposed content of Module 4?*

FDA Response to Question 23:

No, we do not have any comments.

Question 24: *Does the Division have any comments regarding the approach to including additional dose strength data in the asthma application?*

FDA Response to Question 24:

Since the submission and review of data provided in support of NDA 21-936 (Spiriva Respimat Inhalation Spray), a substantial amount of time has passed and we recommend you provide the following in the new NDA (sNDA) submission:

- a. Submit information or data, as appropriate, to each section of e-CTD document for drug substance and drug product. While most of the drug substance data may be referenced to corresponding sections of supporting DMF 21,939 (please provide dates of submission to DMF for supportive data), we request that the current drug substance acceptance specifications be provided in the NDA submission. Also, include batch analysis data representative of drug substance and drug product batches used in the to-be-marketed product and compare the results to the data for drug substance and drug product batches used in the pivotal clinical studies.
- b. Provide updated stability data, with statistical analysis, for drug product batches representative of the to-be marketed product, e.g., three batches for each strength. Provide a comparison and crossreferences to the stability data submitted in support of NDA 21-936 (pivotal clinical and NDA registration stability batches).
- c. Include, in the Quality Summary section, a summary table and explanatory review of all changes implemented to drug product formulation, manufacture, container-closure system and analytical methods in relation to pivotal clinical batches, NDA 21-936 registration and stability, and new NDA (sNDA) registration and stability batches. Provide a clear guide to the reviewer indicating what are the new information and data and include hyperlinks to the NDA submission.
- d. In the interest of facilitating an efficient and timely review of the new strength provide a short narrative in each pertinent section of Module 3 indicating previously submitted data. For example, if some information that supports this new strength is the same as already found acceptable for NDA 21-936 (e.g., excipient controls, analytical methods and validation, container closure components and controls), clearly identify

this information in the submission supporting the new strength such that re-review of already evaluated material is avoided.

- e. Also, refer to our comments (FDA Response to Question 26) in the Advice Letter dated May 10, 2013, for NDA 21-936.

Question 25: *Does the Division agree with the proposed timing for resubmitting a PPSR relative to the submission for patients aged 12 years and older?*

FDA Response to Question 25:

No we do not agree. Submission of a PPSR would be most appropriate after a determination as to the efficacy and safety of tiotropium Respimat has been made in adults and adolescents with asthma. Note that any PPSR should encompass a Pediatric Study Plan that has been agreed to between BI and the Division.

Question 26: *Does the Division have any further comments regarding the clinical studies proposed for issuance of a Written Request?*

FDA Response to Question 26:

See answer to Question 25 above.

Question 27: *Does the Division agree with this proposal?*

FDA Response to Question 27:

Yes, we agree in principle. However, for your proposal to work the COPD indication will need to have been approved and labeling agreed upon.

Question 28: *Does the Division agree with BI's current plan not to submit a REMS in the asthma indication?*

FDA Response to Question 28:

At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks, and if it is necessary, what the required elements will be. We will determine the need for a REMS during the review of your application.

Question 29: *Does the Division agree that separate trade name review submission will not be required for the Spiriva® RESPIMAT in asthma application?*

FDA Response to Question 29:

We disagree; you will need to submit a request for the proprietary name review with this NDA. Please refer to the draft Guidance for Industry, entitled, Contents of a Complete Submission for the Evaluation of Proprietary Names (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>) for the content requirements for such a submission.

Question 30: *Based on this information, does the Division agree that the content and format of the application as described throughout the documents contained herein are adequate to support the review of this submission?*

FDA Response to Question 30:

The adequacy of the content and format for review will be made at the time a filing determination is made.

Question 31: *Does the Division agree that the tiotropium RESPIMAT clinical development program, in light of the data generated to date, will be adequate to assess the dose, dosing frequency, safety and efficacy of once daily (b) (4) tiotropium RESPIMAT for the treatment of asthma in patients 12 years of age and older who remain symptomatic on at least inhaled corticosteroids?*

FDA Response to Question 31:

The adequacy of your program to support your proposed asthma indication will be a review issue.

Question 32: *Does the Division agree the data to be provided in the submission will be sufficient to characterize the pharmacokinetics of tiotropium RESPIMAT in asthma?*

FDA Response to Question 32:

The adequacy of your pharmacokinetics information for tiotropium Respimat in asthma will be a review issue.

Question 33: *Can the Division comment on whether BI should anticipate a PADAC meeting for the tiotropium RESPIMAT asthma indication application?*

FDA Response to Question 33:

While it is premature to comment definitively, pending no major efficacy, safety, or product quality issues, it is likely that a PADAC meeting would be convened.

Additional Clinical Comments:

1. We note that while your Phase 3 clinical trials in severe asthma patients dosed tiotropium Respimat once daily in the AM, your dose interval studies evaluated once daily dosing when administered in the PM. The adequacy of tiotropium Respimat dosed once daily in the PM to support once daily dosing in the AM will be a review issue.
2. We note that the (b) (4) Whether the total daily nominal dose and the dosing frequency of tiotropium in asthma have been adequately assessed or not will also be a review issue.
3. Tiotropium Respimat represents a new class of drug for the treatment of asthma. Whether the relatively small improvement in trough FEV1 observed in asthma patients receiving

tiotropium Respimat in clinical trials is adequate for approval as a bronchodilator will be a review issue.

3.0 **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 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. 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 labeling review resources on the [PLR Requirements of 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, 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. We encourage you to use the SRPI checklist as a quality assurance tool before you submit your proposed PI.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, “Product name, NDA/BLA 012345, Establishment Information for Form 356h.”

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

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/s/

JESSICA K LEE
12/06/2013



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

FACSIMILE TRANSMITTAL SHEET

DATE: June 27, 2008

To: Amy Van Andel, DVM, MPH Senior Associate Director Drug Regulatory Affairs	From: Miranda Raggio, RN, BSN, MA Regulatory Project Manager
Company: Boehringer Ingelheim	Pulmonary and Allergy Products Email: Miranda.Raggio@fda.hhs.gov
Fax number: 203-798-5452	Fax number: 301-796-9728
Phone number: 203-791-6262	Phone number: 301-796-2109

Subject: IND 65127 Meeting Minutes

Total no. of pages including cover: 9

Comments: Please call or send an email to confirm receipt. Thanks, miranda

Document to be mailed: YES xxNO

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FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Meeting Type: B

Meeting Category: End of Phase II

Meeting Date and Time: June 9, 2008 9-10am

Meeting Location: Building 22, Room 1417

Application Number: 65,127

Product Name: Spiriva Respimat (tiotropium bromide inhalation spray)

Received Briefing Package May 7, 2008

Sponsor Name: Boehringer Ingelheim

Meeting Requestor: Amy Van Andel, DVM, MPH, Drug Regulatory Affairs

Meeting Chair: Badrul A. Chowdhury, M.D., Ph.D.,

Meeting Recorder: Miranda J. Raggio, RN, BSN, MA, RPM

Meeting Attendees:

FDA Attendees: Badrul A. Chowdhury, M.D., Ph.D., Division Director, Division of Pulmonary and Allergy Products

Sally Seymour, M.D., Medical Team Leader, Division of Pulmonary and Allergy Products

Banu Karimi Shah, M.D., Medical Reviewer, Division of Pulmonary and Allergy Products

Theresa Michele, M.D., Medical Reviewer, Division of Pulmonary and Allergy Products

Timothy McGovern, Ph.D., Pharmacology/Toxicology Team Leader, Division of Pulmonary and Allergy Products

Luqi Pei, Ph.D., Pharmacology/Toxicology Reviewer, Division of Pulmonary and Allergy Products

Wei Qiu, Ph.D., Acting Clinical Pharmacology Team Leader, Division of Clinical Pharmacology II, Office of Clinical Pharmacology

Yun Xu, Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology II, Office of Clinical Pharmacology

Prasad Peri, Ph.D., Pharmaceutical Assessment Lead, Division of Pre- Marketing Assessment I, Branch II

Qian Li, Sc.D., Biostatistics Team Leader, Office of Biostatistics, Division of Biometrics II

Miranda Raggio, Regulatory Project Manager, Division of Pulmonary and Allergy Products

Sponsor Attendees:

Boehringer Ingelheim:

Chris Corsico, M.D., VP Drug Regulatory Affairs

Bernd Disse, M.D., Ph.D., Therapeutics Area Head, Pulmonary

Petra Moroni-Zentgraf, M.D., International Project Leader, CDept, International Project Management

Michael Engel, M.D., Senior Clinical Research Physician, Respiratory

Ralf Sigmund, Project Statistician

Malcolm Eddie, D.I.B.T, Project Toxicologist

Ashish Sharma, Ph.S. Project Pharmacokineticist

Jeff Snyder, Executive Director, Drug Regulatory Affairs

Amy Van Andel, D.V.M., M.P.H., Senior Associate, Drug Regulatory Affairs

Vittoria Chiesa, Ph.D., Research and Development Project Leader

Pfizer:

Diane Rocco, M.S., M.B.A., Associate Director, U.S. Regulatory Affairs

BACKGROUND

Boehringer Ingelheim (BI) requested a Type B End-of-Phase 2 meeting in a correspondence dated April 7, 2008, received April 8, 2008. The purpose of this meeting was to discuss the proposed Phase 3 trials and development plan for Spiriva Respimat for the treatment of asthma. The meeting package was submitted to the Division on May 7, 2008. Upon review of the meeting package, the Division provided responses to BI via telephone facsimile on June 5, 2008. The content of the telephone facsimile is printed below, with the Division's responses in ***bold italics***. Amy Van Andel, on behalf of BI, sent an email on June 9, 2008, to inform the Division that BI would like to discuss Introductory Comments 1-3, as well as Clinical Questions 1-8 and General Questions 1-3. Summary comments of the meeting discussion are found in *italics* following the facsimile.

INTRODUCTORY STATEMENT

We have the following major concerns with your development program:

- 1. You have not provided any rationale as to why anticholinergics should be efficacious in asthma. Ipratropium bromide is not approved for the treatment of bronchospasm associated with asthma. The benefits of ipratropium bromide in the long-term management of asthma have not been established (GINA 2007). In addition, studies with the Spiriva HandiHaler have not consistently shown benefit in patients with asthma.*
- 2. We expect a full, stand-alone clinical development program for your Spiriva Respimat for the treatment of asthma. Although tiotropium bromide is approved for use in patients with COPD, asthma is a distinctly different disease. Dose and dosing interval cannot be extrapolated to asthma patients. Inclusion of ipratropium into your clinical development plan may also be useful.*
- 3. For an asthma development program, we expect you to address the entire spectrum of asthma severity. We do not agree with limiting your development program to only those patients with severe persistent asthma. Therefore, we would expect you to study a broader spectrum of asthma severity than what you have currently proposed. This information is necessary to appropriately label your drug product. We typically don't label asthma medications for a certain asthma severity.*

While there is no prior precedence for this class of medications to be used for the treatment of asthma either as a rescue medication or as a maintenance/controller medication, (b) (4)

For example, defining a population who remain symptomatic despite optimization of treatment with ICS and LABA may require a run-in period to establish the appropriate population and determine baseline asthma control.

QUESTIONS AND RESPONSES

Clinical

Question 1. BI intends to conduct

(b) (4)

Does the Agency have any comments on this proposal?

Division Response:

(b) (4)

Question 2. The proposed Phase 3 adult clinical development program includes two twin 1-year randomized, double-blind, placebo-controlled, parallel-group design clinical trials in patients with (b) (4) asthma (Trials 205.416 and 205.417). These trials are described in section 9.6, Proposed Phase 3 Development Plan, of the background document. The complete clinical trial protocols are provided in Appendix 12.2 of the background package.

Does the Agency agree with the major points of trial design, including the proposed treatment groups, dose, treatment regimen, statistical analysis plan, and sample size, of the proposed Phase 3 trials (205.416 and 205.417) in patients with (b) (4) asthma?

Division Response: *We do not agree with limiting your development program to (b) (4) asthma and believe the proposed indication is problematic. Therefore, we do not agree with the proposed clinical trials. See the Introductory Comments.*

Question 3. The proposed indication for SPIRIVA RESPIMAT is for the long-term, once-daily

(b) (4)

Does the Agency agree that the primary endpoints identified for the Phase 3 trials (b) (4) (See section 9.6.6, Statistical analysis plan, of the background document and section 7, Statistical Methods, of the Phase 3 clinical trial protocols

Division Response: *We do not agree. As stated above, there is no prior precedence for this class of medications to be used for the treatment of asthma and therefore, the regulatory pathway, including established efficacy variables, has not been determined. In addition, the limited Phase 2 results make it difficult to agree to your proposed efficacy variables. Finally, the efficacy variables may depend in part on your proposed indication and we do not agree with your proposed indication. See the Introductory Comments.*

Question 4. Does the Agency agree that the proposed study population for the Phase 3 program supports the proposed indication statement for (b) (4) asthma? (See section 3.3, Selection of Trial Population, of the Phase 3 clinical trial protocols.)

Division Response: *As proposed, the study population for the Phase 3 program is generally consistent with a (b) (4) asthma population; however, refer to our introductory comment regarding our expectation that you evaluate patients with a spectrum of asthma (b) (4)*

Question 5. BI intends to analyse the time to

(b) (4)

Does the Agency agree with the definition of an asthma exacerbation as described in Section 9.6, Proposed Phase 3 Development Plan?

Division Response: We do not agree. In general, a definition of asthma exacerbation based

(b) (4)

n addition, we do not agree with your definition of severe asthma exacerbation, which is based upon a change in therapy.

Question 6. Does the Agency accept the analysis of the exacerbation data based on the pooled analysis of both trials?

Division:

(b) (4)

Question 7. Does the Agency have any comments on the proposal for the interim analysis?

Division Response: We have general concerns with your clinical development program and proposed clinical trials; therefore we have not provided detailed comments regarding your statistical analysis plan. However, we have the following general comments regarding your analysis plan:

1. For your primary endpoints, clearly specify the missing data imputation strategy.

2. For a

(b) (4)

Question 8. BI intends to characterize the steady-state pharmacokinetics of tiotropium in (b) (4) asthma patient population who will participate in the Phase 3 trials.

Does the Agency agree with this proposal? (See section 9.6.7, Characterization of tiotropium pharmacokinetics in the (b) (4) asthma indication as part of the Phase 3 program, of the background document and sections 5.5, Drug Concentration Measurements – Pharmacokinetics, and 7.3.5, Pharmacokinetic methods, of the Phase 3 clinical trial protocols.)

Division Response: We generally agree with your proposal to characterize tiotropium PK at steady state in severe asthma patients in the Phase 3 trial. To fully characterize tiotropium PK at steady state, drug accumulation at steady state and the time to reach steady state needs to be determined. Since the single dose pharmacokinetics has not been characterized for Spiriva Respimat in this patient population, we recommend you collect plasma and urine samples after the first dose. Based on PK data after a single dose and at steady state, drug accumulation could be determined. In addition, we recommend you collect trough samples at selected days between first dose (Day 1) and the assumed steady state (Day 28) to characterize the actual time to reach steady state.

Non-Clinical

Question 1. No additional pre-clinical pharmacology, pharmacokinetics or toxicology studies are anticipated in support of the proposed indication in adult (b) (4) asthma. (b) (4)

The pre-clinical pharmacology, pharmacokinetics and toxicology of SPIRIVA RESPIMAT are summarized in section 10, Preclinical Data Summary, of the background document.

Does the Agency agree that no additional preclinical toxicology studies are required to initiate the proposed Phase 3 program?

Division Response: Yes, we agree.

Question 2. (b) (4)

Division Response: (b) (4)

Question 3. The proposed formulation for indented market approval will be used in the Phase 3 clinical program and is identical to that used in Phase 3 clinical trials for COPD indication (reference: SPIRIVA RESPIMAT NDA 21-936 currently under FDA review.) Information on the drug substance and drug product is provided in section 11, Chemistry, Manufacturing and Controls Information, of the background document.

Does the Agency agree that no additional CMC data other than that filed and updated for SPIRIVA RESPIMAT COPD indication will be needed for registration.

Division Response: No, we do not agree. Demonstration of stability of the drug substance in the (b) (4) as suggested in IND (b) (4) may not be sufficient for a solution formulation. Our concern is that there may be different stability kinetics for the impurities obtained by the new route of synthesis. The absence of these differences will need to be demonstrated in your development report/NDA/supplement. Provide results for the drug product using the drug substance manufactured by the new route of synthesis in the NDA.

In addition to addressing the comments provided in the August 2, 2007, meeting minutes, we recommend that you utilize the drug substance with the new route of synthesis in Phase 3 studies and stability studies to be provided for the NDA/supplement.

The new route of synthesis may be incorporated in the current DMF for tiotropium bromide as an amendment.

General

Question 1. An overview of clinical data, including previous human experience with tiotropium in asthma, the Phase 2 trial 205.341 and the Phase 3 development plan are provided in section 2, Clinical Data Summary, of the background document. The draft synopsis of the completed clinical trial, 205.341; the clinical trial protocols for the proposed Phase 3 trials, 205.416 and 205.417; and the proposed draft US Package Insert including the asthma indication are provided in the Appendix (section 12).

Does the Agency agree that data from the two independent Phase 3 trials (205.416 and 205.417), and the supportive data from the completed Phase 2 proof-of-concept trial (205.341) and the FEV₁ AUC (0-3h) and FEV₁ trough measurements in the Phase 3 Trials 205.416 and 205.417 will provide adequate information to establish the safety and efficacy?

Division Response: We do not agree. See the Introductory Comments.

Question 2. Does the Agency agree that data from 67 patients who underwent 24-hour lung function measurement in the proof-of-concept trial (205.341) provide sufficient evidence for a sustained effect over 24 hours for tiotropium administered as an once-daily treatment drug?

Division Response: We do not agree. You will need to provide 24-hour spirometry as a part of your Phase 3 development program.

Question 3. BI proposes to submit the (b) (4) tiotropium RESPIMAT in (b) (4) asthma based on data from approximately 300 patients on once-daily tiotropium RESPIMAT for 12 months from the planned Phase 3 trials.

Does the Agency agree that a submission with 12-month exposure in the target asthma population will be adequate to support the review of the sNDA?

Division Response: We do not agree. Generally, asthma development programs tend to be larger in number, given the wide spectrum of asthma disease. In addition, a larger safety database may be required if a safety signal is noted in your development program.

DISCUSSION HIGHLIGHTS

The following statements summarize the major points discussed:

1. *BI began the discussion by asking the Division to clarify the general intent of the Introductory Comments with regard to the tiotropium asthma development program. The Division restated their major concerns:*
 - a. *Spiriva HandiHaler studies to date have not found tiotropium bromide to be efficacious in the asthma population.*
 - b. *Ipratropium bromide, a short-acting anticholinergic, has not shown efficacy and is therefore not approved for the treatment of bronchospasm associated with asthma. As a result, the BI development program lacks a supporting foundation from which to progress. The Division cited the example of the long-acting beta agonists (LABAs), which were supported by the knowledge and efficacy data for the short acting beta-agonists in patients with asthma. The historical data with ipratropium and the lack of scientific data regarding the use of anticholinergics in asthma are issues that do not support this development program.*
 - c. *A development program for asthma must be a complete, stand-alone clinical program which recognizes asthma as a distinctly different disease from COPD for which tiotropium is approved. The Sponsor proposed that cholinergic tone plays a larger role in severe asthma, in which there might be less airway reversibility to beta-*

agonists, but from a regulatory standpoint, the Division noted that these patients with burned out asthma may be difficult to differentiate from patients with COPD.

- d. The entire spectrum of asthma severity must be addressed in an asthma development program in order to appropriately label the tiotropium product. Current guidelines suggest studying all degrees of asthma severity unless scientific rationale and evidence shows otherwise. BI has not provided such rationale and/or evidence. The Division would generally expect a drug to work for the entire spectrum of asthma severity unless there is a good scientific rationale why it only works in severe asthma. It is not clear why tiotropium would work in severe asthma and not other asthma severities. The Division stated that limiting the study of a drug to a particular severity of asthma is problematic, as the severity of the disease is constantly in flux.*

(b) (4)

- 2. BI stated that expert panels indicated that tiotropium is beneficial in patients with severe asthma and this was the basis of the proof of concept study and the development program. The Division stated that anecdotal experience of off-label use of tiotropium as a bronchodilator for severe asthma symptoms by expert panels assembled by the Sponsor is not sufficient to provide a basis for an asthma indication.*
- 3. BI noted that they have information with the use of Spiriva HandiHaler in patients with mild to moderate asthma and the data was not supportive. BI stated that they would likewise not expect Spiriva Respimat to show benefit in these population and they may have a difficult time getting approval from IRBs for such a study. The Division informed BI that generalizing assumptions regarding dose, dosing interval and efficacy from the HandiHaler to the Respimat device is inappropriate. The Spiriva HandiHaler and Spiriva Respimat are two different drug products utilizing two different delivery devices, and thus determination of the dosing regimen and efficacy must be independently established.*
- 4. The Division expressed strong concern regarding BI's intent to link Spiriva HandiHaler and Respimat by pharmacokinetic data, and informed BI that this approach is not acceptable for locally-active drug products. The Division also stated that pharmacokinetic data from healthy volunteers could not be extrapolated to asthma and COPD patients. BI inquired about the acceptability of comparing pharmacokinetic data from asthma and COPD patients. The Division responded that because pharmacokinetic data from a COPD population can not be generalized to an asthma population, the PK profile of tiotropium in patients with asthma should be established. BI inquired if it is acceptable to only collect the pharmacokinetic data at day 28 because Spiriva is a chronic use drug and the pharmacokinetics profile at steady state is more relevant. The Division emphasized that to fully characterize tiotropium PK at steady state, drug accumulation at steady state and the time to reach steady state need to be determined. The Division recommended to collect plasma and urine samples after the first dose, and collect trough samples at selected days between first dose (Day 1) and the assumed steady state (Day 28). BI asked if it is acceptable to collect trough concentrations at Day 7, 14, and 21. The Division agreed that this was an acceptable approach.*
- 5. The Division stated that the science may have to change in order to support the clinical program as we don't have answers to some of the questions raised during the discussion. The Division noted that there are no safety concerns with the proposed clinical trial, however, it*

is important for BI to understand the Division's concerns with the development program. The Division noted that the concerns with the program are not merely labeling concerns, but are approvability issues.

6. *BI asked if data from clinical trials conducted to evaluate the effectiveness of tiotropium as a bronchodilator in asthma patients could be submitted to the Division for review. The Division responded affirmatively.*

If you have any questions, please contact Miranda Raggio, Regulatory Project Manager, at 301-796-2109.

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Linked Applications

Sponsor Name

Drug Name

IND 65127

BOEHRINGER
INGELHEIM
PHARMACEUTICALS
INC

RESPINAT/SPIRIVA(TIOTROPIUM
BROMIDE)INH

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/s/

MIRANDA B RAGGIO
06/26/2008