

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
021936Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 21936

SUPPL #

HFD #

Trade Name Spiriva Respimat

Generic Name tiotropium inhalation spray

Applicant Name Boehringer Ingelheim Pharmaceuticals, Inc.

Approval Date, If Known September 24, 2014

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES NO

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

505(b)(1)

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

YES NO

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

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

d) Did the applicant request exclusivity?

YES X NO

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

3 Years

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

YES NO X

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# 21395

Spiriva HandiHaler (Tiotropium bromide inhalation powder)

NDA#

NDA#

2. Combination product.

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

YES NO

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

NDA#

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 X

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:

205.251, 205.252, 205.254, 205.255, 205.372, 205.452

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

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

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

Investigation #1 YES NO

Investigation #2 YES NO X

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

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

Investigation #1 YES NO

Investigation #2 YES NO X

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"):

205.251, 205.252, 205.254, 205.255, 205.372, 205.452

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

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

Investigation #1
IND # 65127 YES ! NO
! Explain:

Investigation #2
IND # 65127 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 Lee, Pharm.D.
Title: Regulatory Health Project Manager
Date: September 12, 2014

Name of Division Director signing form: Badrul Chowdhury, M.D.,Ph.D.
Title: Division 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
09/24/2014

BADRUL A CHOWDHURY
09/24/2014

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 21-936 Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: 11-16-07 PDUFA Goal Date: 9-16-08

HFD 570 Trade and generic names/dosage form: SPIRIVA Respimat (tiotropium bromide) Nasal Spray

Applicant: Boehringer Ingelheim Therapeutic Class: Respiratory

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

- Yes. Please proceed to the next question.
 No. PREA does not apply. Skip to signature block.

* SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.

Indication(s) previously approved (please complete this section for supplements only): _____

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): one

Indication #1: Maintenance treatment of bronchospasm associated with COPD

Is this an orphan indication?

- Yes. PREA does not apply. Skip to signature block.
 No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
 No: Please check all that apply: ___Partial Waiver ___Deferred ___Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
 Disease/condition does not exist in children
 Too few children with disease to study
 There are safety concerns
 Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

NDA 21-936

Page 3

This page was completed by:

{See appended electronic signature page}

Miranda Raggio, RN, BSN, MA

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is this an orphan indication?

- Yes. PREA does not apply. Skip to signature block.**
- No. Please proceed to the next question.**

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.**
- No: Please check all that apply: ___Partial Waiver ___Deferred ___Completed**

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population**
- Disease/condition does not exist in children**
- Too few children with disease to study**
- There are safety concerns**
- Other: _____**

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below)::

Min _____	kg _____	mo. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population**
- Disease/condition does not exist in children**
- Too few children with disease to study**
- There are safety concerns**
- Adult studies ready for approval**
- Formulation needed**
- Other: _____**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is

complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below)::

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

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

/s/

Miranda Raggio
2/13/2008 02:21:24 PM

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 21936 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:
❖ Actions		
<ul style="list-style-type: none"> Proposed action User Fee Goal Date is <u>9/24/14</u> 		X AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> Previous actions <i>(specify type and date for each action taken)</i> 		<input type="checkbox"/> None CR 9/16/08
❖ 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 Characteristics³		

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, (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: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	<input type="checkbox"/> Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input 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 (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters <i>(including approval letter with final labeling)</i>	Action(s) and date(s) CR 9/16/08 AP 9/24/14
Labeling	
❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	
<ul style="list-style-type: none"> • Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i> 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included 11/16/07; 3/24/14
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling <i>(write submission/communication date at upper right of first page of each piece)</i>	<input 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
<ul style="list-style-type: none"> • Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i> 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included
❖ Labels (full color carton and immediate-container labels) <i>(write submission/communication date on upper right of first page of each submission)</i>	
<ul style="list-style-type: none"> • Most-recent draft labeling 	<input checked="" type="checkbox"/> Included
❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i> • Review(s) <i>(indicate date(s))</i> 	Acceptable 7/1/14 6/30/14
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: <input type="checkbox"/> None 2/13/08; 5/2/14 DMEPA: <input type="checkbox"/> None 7/14/14 DMPP/PLT (DRISK): <input type="checkbox"/> None 7/31/08; 8/28/14 OPDP: <input type="checkbox"/> None 2/12/08; 8/28/14 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Other: <input checked="" type="checkbox"/> None
Administrative / Regulatory Documents	
❖ Administrative Reviews <i>(e.g., RPM Filing Review⁴/Memo of Filing Meeting) (indicate date of each review)</i>	2/13/08
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Committee	<input type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary <i>(signed by Division Director)</i>	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

⁴ Filing reviews for scientific disciplines should be filed with the respective discipline.

<ul style="list-style-type: none"> This application is on the AIP <ul style="list-style-type: none"> If yes, Center Director's Exception for Review memo (<i>indicate date</i>) If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> Date reviewed by PeRC <u>5/21/14</u> If PeRC review not necessary, explain: _____ 	5/8/08
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters) (<i>do not include previous action letters, as these are located elsewhere in package</i>)	11/28/07; 2/4/08; 3/13/08; 3/26/08; 4/24/08; 5/27/08; 6/18/08; 7/7/08; 7/8/08; 7/15/08; 7/18/08; 7/22/08; 8/4/08; 4/4/14; 4/4/14; 5/2/14; 5/15/14; 6/6/14; 6/11/14; 7/15/14; 8/7/14; 8/12/14; 8/19/14; 9/2/14; 9/17/14; 9/18/14; 9/23/14
❖ 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)	7/22/08; 7/31/08; 8/4/08
❖ Minutes of Meetings	
<ul style="list-style-type: none"> If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> No mtg 4/20/05
<ul style="list-style-type: none"> EOP2 meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> No mtg
<ul style="list-style-type: none"> Mid-cycle Communication (<i>indicate date of mtg</i>) 	<input type="checkbox"/> N/A
<ul style="list-style-type: none"> Late-cycle Meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> N/A
<ul style="list-style-type: none"> Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>) 	2/29/08; Reg Briefing 7/18/08
❖ Advisory Committee Meeting(s)	<input type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> Date(s) of Meeting(s) 	8/14/14
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 9/16/08; 9/24/14
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 8/22/08; 9/11/14
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None
Clinical	
❖ Clinical Reviews	
<ul style="list-style-type: none"> Clinical Team Leader Review(s) (<i>indicate date for each review</i>) 	<input type="checkbox"/> No separate review
<ul style="list-style-type: none"> Clinical review(s) (<i>indicate date for each review</i>) 	1/16/08; 7/31/08; 8/28/14
<ul style="list-style-type: none"> Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	<input type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	MO Review 7/31/08; 8/28/14
❖ 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 checked="" type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input type="checkbox"/> None requested 7/31/08
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 8/26/08; 8/29/14; 8/29/14
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 7/10/08; 7/31/08; 8/29/14
❖ 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 7/31/08; 9/3/14
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None 1/23/08; 7/29/08; 8/26/14
❖ 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 1/29/08; 2/18/08; 5/20/08; 8/15/08; 7/25/14; 9/22/14
❖ Microbiology Reviews		<input type="checkbox"/> Not needed 7/3/08; 8/14/08; 8/22/14
<input checked="" 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>		
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>		<input type="checkbox"/> None P/T 5/6/08; CDRH 6/1/08; 7/15/14; CDRH 8/28/14
❖ 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>		11/6/07
<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: <input checked="" type="checkbox"/> Acceptable 3/7/08; 9/11/14 <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 checked="" 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	
<ul style="list-style-type: none"> ❖ 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
<ul style="list-style-type: none"> ❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email 	<input type="checkbox"/> Done
<ul style="list-style-type: none"> ❖ 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
<ul style="list-style-type: none"> ❖ 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
<ul style="list-style-type: none"> ❖ Ensure Pediatric Record is accurate 	<input type="checkbox"/> Done
<ul style="list-style-type: none"> ❖ Send approval email within one business day to CDER-APPROVALS 	<input type="checkbox"/> Done

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/s/

JESSICA K LEE
09/24/2014



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

ELECTRONIC CORRESPONDENCE

DATE: September 23, 2014

To: Ingeborg Arny-Cornejo, MD Sr. Associate Director Regulatory Affairs	From: Jessica Lee, PharmD Regulatory Project Manager
Company: Boehringer Ingelheim	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: 203-791-6262	Fax number: 301-796-9728
Phone number: 203-798-9988	Phone number: 301-796-3769
Subject: NDA 21936 Labeling #3	

Total no. of pages including cover:

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Dear Dr. Arny-Cornejo:

Your submission dated, March 24 and May 23, 2014, to NDA 21936, is currently under review. Attached are our revisions, made as track changes to the clean version of your proposed package insert (PI) and Instructions for Use (IFU) submitted September 19, 2014. Be advised that these labeling changes are not the Agency's final recommendations and that additional labeling changes may be forthcoming as the labeling review continues.

We request you address the edits and submit the corrected label. Use the FDA clean version to submit any proposed changes and submit a clean and track-change versions of the label. 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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JESSICA K LEE
09/23/2014



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

ELECTRONIC CORRESPONDENCE

DATE: September 18, 2014

To: Ingeborg Arny-Cornejo, MD Sr. Associate Director Regulatory Affairs	From: Jessica Lee, PharmD Regulatory Project Manager
Company: Boehringer Ingelheim	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: 203-791-6262	Fax number: 301-796-9728
Phone number: 203-798-9988	Phone number: 301-796-3769

Subject: NDA 21936 Labeling #2 addition

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NDA 21936

Dear Dr. Army-Cornejo:

Your submission dated September 10, 2014, to NDA 21936, is currently under review. We have the following addition to the September 17, 2014 labeling information request that was sent to you on September 17, 2014:

Incorporate the following under section 12.3:

"A dedicated pharmacokinetic study in patients with COPD evaluating once-daily tiotropium delivered from the RESPIMAT® inhaler (5µg) and as inhalation powder (18µg) from the HandiHaler® resulted in a similar systemic exposure between the two products."

We request you add the above comment to the NDA 21936, Spiriva Respimat, label and respond to September 17, 2014 labeling information request by Friday, September 19, 2014. Use the FDA clean version to submit any proposed changes and submit a clean and track-change versions of the label. 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
09/18/2014



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

ELECTRONIC CORRESPONDENCE

DATE: September 17, 2014

To: Ingeborg Arny-Cornejo, MD Sr. Associate Director Regulatory Affairs	From: Jessica Lee, PharmD Regulatory Project Manager
Company: Boehringer Ingelheim	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: 203-791-6262	Fax number: 301-796-9728
Phone number: 203-798-9988	Phone number: 301-796-3769

Subject: NDA 21936 Labeling #2

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Dear Dr. Army-Cornejo:

Your submission dated September 10, 2014, to NDA 21936, is currently under review. Attached are our revisions, made as track changes to the clean version of your proposed package insert (PI) and Instructions for Use (IFU). Be advised that these labeling changes are not the Agency's final recommendations and that additional labeling changes may be forthcoming as the labeling review continues. The major changes were primarily in sections 6, 8, 12, 13, and 14 of the label and included the following:

Section 6

- We have allowed pooling of safety data from the 7-trial safety database. However, we have added the number and percent of deaths that occurred in Spiriva Respimat 5mcg and placebo patients. Verify these numbers. We also refer the reader to section 14 for information regarding the mortality trial.
- We have allowed postmarketing information in newly created section 6.2 Postmarketing Experience

Section 8 and 13

- The ratios used to express non-clinical safety margins in these sections were changed to be consistent with the Spiriva HandiHaler label. Spiriva Respimat and Spiriva HandiHaler labeling should have the same tiotropium exposure ratios for their nonclinical sections based on clinical pharmacokinetic data. The two products produced similar systemic exposures of tiotropium although they have a 3.6-fold difference in the maximum recommended daily inhalation dose (MRHDID) in tiotropium. Tiotropium MRHDIDs are 5 and 18 mcg for Respimat and HandiHaler, respectively. The respective steady state pharmacokinetic parameters of Respimat (5-mcg tiotropium) and HandiHaler (18-mcg tiotropium) in humans were 24.4 and 32.1 ng.h/mL in mean AUC_{0-6} and 12.4 and 15.4 ng/L in C_{max} . The lack of difference in tiotropium systemic exposures between the products in humans indicates that it is inappropriate for their labeling to use different dose multiples, especially to increase the exposure multiples in the HandiHaler labeling by 3.6 to obtain ratios for the Respimat labeling. Also, if the nonclinical sections of tiotropium product labels are harmonized in the future, the HandiHaler ratios, representing the most conservative dose ratios, will be used.

Section 12

- We have reformatted this section. Changes were made to this section to reflect the new FDA guidance for Clinical Pharmacology labeling (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm109739.pdf>). This new guidance defines a different structure for section 12 (especially 12.3) compared to the previous version.

Section 14

- We have removed [REDACTED] (b) (4)
- We have allowed for pooling of results from trials 205.254 and 205.255 for the COPD exacerbation claim. [REDACTED] (b) (4)
- We have removed reference to [REDACTED] (b) (4), as the inclusion [REDACTED] (b) (4) provide little additional above that already presented from trials 205.251, 205.252, 205.254, 205.255, and 205.372 which were longer and larger.
- We have removed reference to [REDACTED] (b) (4) from the dose-ranging section [REDACTED] (b) (4). Additionally, the proposed dose of Spiriva Respimat was confirmed in trials 205.251, 205.252, 205.254, 205.255, and 205.372.
- We have included the rationale for the use of Spiriva HandiHaler as the active comparator in the description of TIOSPIR.
- Given the concern regarding myocardial infarction (MI) voiced at the Spiriva Respimat Advisory committee and by some in the scientific community, we have included fatal MI data from TIOSPIR in the label. We have added additional language to place into context.

Other changes were also made and where appropriate, an explanation was included as a comment. In addition to the tracked changes edits, we also ask that you make the following changes:

- Amend table 1 such that the rows for “cough” and “sinusitis” are aligned, and add a footnote to indicate that the adverse reaction terms were groupings of similar terms
- Reformat Figure 1 such that the axes titles and units are legible, and legend to replace “Tio R 5” with “SPIRIVA RESPIMAT 5mcg.”
- Amend table 2 to include 2 additional columns with the N’s for the Spiriva Respimat 5 mcg and placebo treatment groups. In you proposed table, inclusion of “N” for each treatment group in parentheses under the trial numbers makes the table difficult to read.

We request you address the edits and submit the corrected label by Friday, September 19, 2014. Use the FDA clean version to submit any proposed changes and submit clean and track-change versions of the label. 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
09/17/2014



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

ELECTRONIC CORRESPONDENCE

DATE: September 2, 2014

To: Ingeborg Arny-Cornejo, MD Sr. Associate Director Regulatory Affairs	From: Jessica Lee, PharmD Regulatory Project Manager
Company: Boehringer Ingelheim	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: 203-791-6262	Fax number: 301-796-9728
Phone number: 203-798-9988	Phone number: 301-796-3769

Subject: NDA 21936 Labeling

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Dear Dr. Army-Cornejo:

Your submission dated, March 24 and May 23, 2014, to NDA 21936, is currently under review. Attached are our revisions to your proposed package insert (PI) and Instructions for Use (IFU). Changes to your submitted label were made according to current labeling practices for newer long-acting bronchodilator medications, including anticholinergic bronchodilators. 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. The major changes were primarily in sections 6 and 14 of the label and included the following:

Section 6

- The adverse event table (Table 1) was revised to include data from the three forty-eight trials only (205.254, 205.255, and 205.372). This revision was made as these trials were similar in design, duration, and patient population.

Section 14

- Table 2 was added to summarize the results for the spirometric primary endpoints in Trials 205.251, 205.252, 205.254, 205.255, and 205.372.

(b) (4)

- A new Figure 1 was added to portray SPIRIVA RESPIMAT's effect on trough FEV1 over the 48-week treatment period. This figure should be updated to a black and white image, where the x-axis is in weeks and the y-axis in liters. The appearance and format should be similar to proposed Figure 3.

(b) (4)

- A new Table 3 was added summarize the mortality data from TIOSPIR.

Instructions for Use:

- Change the font of the Instructions for Use to Verdana 11 point font.

We request you address the deficiencies/edits and submit the corrected label by COB, Friday, September 5, 2014. Use the FDA clean version to submit any proposed changes and submit clean and track-change versions of the label. 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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JESSICA K LEE
09/02/2014



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

ELECTRONIC CORRESPONDENCE

DATE: August 19, 2014

To: Ingeborg Arny-Cornejo, MD Sr. Associate Director Regulatory Affairs	From: Jessica Lee, PharmD Regulatory Project Manager
Company: Boehringer Ingelheim	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: 203-791-6262	Fax number: 301-796-9728
Phone number: 203-798-9988	Phone number: 301-796-3769

Subject: Information Request

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Dear Dr. Army-Cornejo:

Your submission dated, March 24, 2014, to NDA 21936, is currently under review. We have the following requests for information:

- 1.) Provide pooled baseline demographic, pulmonary function, and concomitant medication information in patients in the three 48-week trials (205.254, 205.255, 205.372) by treatment group. Additionally, provide numbers and percentages for discontinuations due to adverse events for patients who received Spiriva Respimat 5mcg and placebo.
- 2.) For the pooled safety data from trials 205.254, 205.255, and 205.372, provide a table that includes adverse events that occurred in $\geq 2\%$ of patients who received Spiriva Respimat 5mcg and were higher than placebo. Express events in terms of system organ class and preferred term.
- 3.) In section 6 of your proposed label, you have the following statements:

“Other reactions that occurred in the SPIRIVA RESPIMAT group at an incidence of 1% to 3%, and at a higher incidence rate on SPIRIVA RESPIMAT than on placebo included: *Cardiac disorders*: palpitations; *Gastrointestinal disorders*: constipation; gastroesophageal reflux disease; oropharyngeal candidiasis; *Nervous system disorders*: dizziness; *Respiratory system disorders (Upper)*: dysphonia; *Skin and subcutaneous tissue disorders*: pruritus, rash; *Renal and urinary disorders*: urinary tract infection.

Less Common Adverse Reactions

(b) (4) among the adverse reactions observed in the clinical trials with an incidence of $< 1\%$ and at a higher incidence rate on SPIRIVA RESPIMAT than on placebo were: (b) (4): dysphagia, gingivitis, intestinal obstruction including ileus paralytic; (b) (4): joint swelling; (b) (4): dysuria, urinary retention; (b) (4): epistaxis, laryngitis; (b) (4): angioedema, dry skin, skin infection and skin ulcer.”

Update these statements to reflect the data from the pooled 48-week trials.

- 4.) Provide pooled baseline demographic and pulmonary function information for the two 12-week trials (205.251 and 205.252) by treatment group.
- 5.) Provide a figure depicting trough FEV1 over time for trial 205.254. Do the same for trials 205.255, and 205.372. Provide in a format similar to your Advisory Committee slide CE-9.
- 6.) For trial 205.249, provide a figure depicting mean FEV1 at each time point (prior to and after administration of trial drug) on Day 29. Exclude the Spiriva Handihaler data from the figure.

- 7.) For trial 205.127, provide the 95% confidence intervals marked as “XX, XX” in the table below.

Trial 205.127. Trough FEV1 dose response results

Treatment group	N	Mean Trough FEV1 (L) Response on day 21	Difference from placebo (L) (95% CI)
Spiriva Respimat 1.25 mcg qD	25	0.10	(XX,XX)
Spiriva Respimat 2.5 mcg qD	28	0.05	(XX,XX)
Spiriva Respimat 5 mcg qD	25	0.15	(XX,XX)
Spiriva Respimat 10 mcg qD	26	0.13	(XX,XX)
Spiriva Respimat 20 mcg qD	26	0.15	(XX,XX)
Placebo Respimat qD	24	0.02	
Spiriva Handihaler 18 mcg qD	25	0.23	(XX,XX)
Handihaler Placebo	23	-0.09	

Submit responses to the NDA by Thursday, August 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.

NDA 21936

Drafted by: BLim/Aug 19, 2014
JLee/Aug 19, 2014

Initialed by: LJafari/ Aug 19, 2014

Finalized by: JLee/Aug 19, 2014

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/s/

JESSICA K LEE
08/19/2014



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

ELECTRONIC CORRESPONDENCE

DATE: August 12, 2014

To: Ingeborg Arny-Cornejo, MD Sr. Associate Director Regulatory Affairs	From: Jessica Lee, PharmD Regulatory Project Manager
Company: Boehringer Ingelheim	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: 203-791-6262	Fax number: 301-796-9728
Phone number: 203-798-9988	Phone number: 301-796-3769

Subject: Information Request

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Dear Dr. Army-Cornejo:

Your submission dated, March 24, 2014, to NDA 21936, is currently under review. We have the following requests for information:

1. Provide the total MACE analysis for UPLIFT, or clarify if that is what was provided in tables 4.4.1 under the columns “HANDIHALER 1 study” in your most recent submission. If table 4.4.1 is a total MACE analysis of UPLIFT, clarify why the number of patients with fatal MI is different compared to table 30 of the advisory committee briefing package.
2. Clarify the discrepancy of number of events for fatal MACE (CV death) on table 2.5.11 of the scs supplement (Placebo= 15, Spiriva Respimat=26) and table 34 of the AC briefing package (Placebo= 14, Spiriva Respimat=25) for the vital status database (4-studies).
3. Clarify if the cardiovascular death definition used in table 34 of the advisory committee briefing package includes deaths in the stroke PVE and the SMQ ischemic heart disease sub-SMQ myocardial infarction.

Submit your responses as soon as possible today, August 12, 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.

NDA 21936

Drafted by: BLim/August 11, 2014
JLee/August 12, 2014

Initialed by: LJafari/ Aug 12, 2014

Finalized by: JLee/Aug 12, 2014

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/s/

JESSICA K LEE
08/12/2014



**Food and Drug Administration
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ELECTRONIC CORRESPONDENCE

DATE: August 7, 2014

To: Ingeborg Arny-Cornejo, MD Sr. Associate Director Regulatory Affairs	From: Jessica Lee, PharmD Regulatory Project Manager
Company: Boehringer Ingelheim	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: 203-791-6262	Fax number: 301-796-9728
Phone number: 203-798-9988	Phone number: 301-796-3769

Subject: Information Request

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Dear Dr. Arny-Cornejo:

Your submission dated, March 24, 2014, to NDA 21936, is currently under review. We have the following requests for information:

We request that you submit the following information using “**on-treatment + 30 day**” observation window:

1. Transient ischemic attacks (TIA) are not always included in MACE analysis. You have included the TIA outcome event in your composite MACE analysis in TIOSPIR. Provide an additional composite MACE analysis excluding the TIA outcome. Specifically, provide number of first occurrence of events by treatment using a composite MACE definition defined as any of the following components:
 - myocardial infarction (includes fatal and non-fatal outcome event)
 - stroke (includes fatal and non-fatal outcome event)
 - cardiovascular death (i.e., any deaths within SOC ‘Cardiac disorders’, deaths designated as PTs ‘cardiac death’, ‘sudden death’, or ‘sudden cardiac death’ within SOC ‘General disorders and administration site conditions’; and any deaths within SOC ‘Vascular disorders’, per adjudicated cause of death)

Include the hazard ratio estimate along with its 95% confidence interval for the MACE composite endpoint defined as above. Present this data in a similar format to tables 34 and 35 of your Advisory Committee briefing package.

2. In TIOSPIR, for the outcome events of stroke and myocardial infarction, you have presented the data in terms of all events (fatal and non-fatal). For these outcome events, provide a breakdown of these outcome events into fatal and non-fatal events. Specifically, provide the following information for myocardial infarction and stroke outcome events:
 - Number of first occurrence of **non-fatal** outcome event by treatment and the hazard ratio estimate along with its 95% confidence interval for **non-fatal** outcome events.
 - Number of **fatal** outcome event by treatment and the hazard ratio estimate along with its 95% confidence interval for **fatal** outcome event
3. In the analysis of MACE and MACE components for the placebo controlled clinical safety database (7-studies) provided on table 2.5.11 and 2.5.12 of the scs-supplement study body report (pg 572 and 573), for the stroke PVE and SMQ ischemic heart disease sub-SMQ myocardial infarction you have only provided the data for total events. Provide analysis of MACE and MACE components for the placebo controlled clinical safety database (7-studies) where events in the stroke PVE and SMQ ischemic heart disease sub-SMQ myocardial infarction are sub-divided into fatal and non-fatal events. Additionally, provide a similar analysis of all MACE (fatal and non-fatal) for the placebo controlled vital status database (4-studies). Also, provide an additional composite MACE analysis excluding the preferred term transient ischemic attack for both the clinical safety and vital status databases.

NDA 21936

Submit responses to the NDA by noon, Monday, August 11, 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.

NDA 21936

Drafted by: RLim/8.7.14
JLee/8.7.14

Initialed by: LJafari/8.7.14
ADurmowicz/8.7.14

Finalized by: JLee/8.7.14

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/s/

JESSICA K LEE
08/07/2014



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

ELECTRONIC CORRESPONDENCE

DATE: July 15, 2014

To: Ingeborg Arny-Cornejo, MD Sr. Associate Director Regulatory Affairs	From: Jessica Lee, PharmD Regulatory Project Manager
Company: Boehringer Ingelheim	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: 203-791-6262	Fax number: 301-796-9728
Phone number: 203-798-9988	Phone number: 301-796-3769

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Dear Dr. Arny-Cornejo:

Your submission dated, March 24, 2014, to NDA 21936, is currently under review. We have the following request for information from reviewers at the Center for Devices and Radiological Health (CDRH):

You indicate that you have received 22 complaints or device malfunctions in the clinical phase 3 studies conducted for RESPIMAT A4 inhalers and corrective actions were implemented. However, you have not provided detailed information regarding the malfunctions reported or the corrective actions which were put in place. Furthermore, you indicate you have also received 16 complaints or device malfunctions in your larger Phase 3b studies conducted with SPIRIVA RESPIMAT (*e.g.*, study 205.452) after the 2007 NDA submission. While you indicate that the rate of complaints has been reduced, you have not provided any information on the events reported in the larger Phase 3b study. It is unclear whether these are similar events as seen in the previous studies or if new types of events have occurred. You have also not specified whether any attempt has been made to further mitigate these issues. Provide a detailed discussion of all malfunctions and complaints reported as well as the mitigation strategies implemented. Clarify whether any of the corrective actions implemented required a modification in device design.

Submit a response to the NDA by July 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.

NDA 21936

Drafted by: JLee/July 14, 2014

Initialed by: LJafari/July 14, 2014
ADurmowicz/July 14, 2014

Finalized by: JLee/July 15, 2014

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/s/

JESSICA K LEE
07/15/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 21936

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

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

ATTENTION: Ingeborg Army-Cornejo, MD
Senior Associate Director, Drug Regulatory Affairs

Dear Dr. Army-Cornejo:

Please refer to your New Drug Application (NDA) dated March 24, 2014, received March 24, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tiotropium Bromide Inhalation Spray, 2.5 mcg per actuation.

We also refer to your April 14, 2014, correspondence, received April 14, 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 April 14, 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/

TODD D BRIDGES on behalf of KELLIE A TAYLOR
07/01/2014



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

ELECTRONIC CORRESPONDENCE

DATE: June 11, 2014

To: Ingeborg Arny-Cornejo, MD Sr. Associate Director Regulatory Affairs	From: Jessica Lee, PharmD Regulatory Project Manager
Company: Boehringer Ingelheim	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: 203-791-6262	Fax number: 301-796-9728
Phone number: 203-798-9988	Phone number: 301-796-3769

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NDA 21936

Dear Dr. Arny-Cornejo:

Your submission dated, March 24, 2014, to NDA 21936, is currently under review. We have the following request for information:

We note that you have not supplied a patient package insert (PPI) for your Spiriva Respimat in your complete response NDA submission. Please let us know if you plan to include a PPI for the Spiriva Respimat product.

Submit responses to the NDA by the close of business, Monday, June 16, 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.

NDA 21936

Drafted by: JLee/June 11, 2014

Initialed by: LJafari/ June 11, 2014

Finalized by: JLee/June 11, 2014

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/s/

JESSICA K LEE
06/11/2014



Food and Drug Administration
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 Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

DATE: June 6, 2014

To: Ingeborg Arny-Cornejo, MD Sr. Associate Director Regulatory Affairs	From: Jessica Lee, PharmD Regulatory Project Manager
Company: Boehringer Ingelheim	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: 203-791-6262	Fax number: 301-796-9728
Phone number: 203-798-9988	Phone number: 301-796-3769
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Dear Dr. Army-Cornejo:

Your submission dated, March 24, 2014, to NDA 21936, is currently under review. We have the following request for information:

For Clinical Study 205.452, submit exacerbation datasets similar to the exacerbation datasets in study 205.372. Specifically datasets that include time to first COPD exacerbation, time to first hospitalization due to COPD exacerbation, time to first moderate to severe COPD exacerbation, and exacerbation rates. Provide detailed descriptions for all of your exacerbation efficacy datasets and the variables used in your efficacy analyses. Also provide all program code used for these analyses.

Submit responses to the NDA by the close of business, Monday, June 9, 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.

NDA 21936

Drafted by: KHamilton/June 6, 2014
JLee/June 6, 2014

Initialed by: LJafari/June 6, 2014

Finalized by: JLee/June 6, 2014

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/s/

JESSICA K LEE
06/06/2014

PeRC PREA Subcommittee Meeting Minutes
May 21, 2014

PeRC Members Attending:

Lynne Yao

Dianne Murphy

George Greeley

Hari Cheryl Sachs

Karen Davis-Bruno (did not review Flebogamma)

Andrew Mosholder

Lily Mulugeta

Robert "Skip" Nelson

Daiva Shetty

Gregory Reaman

Rosemary Addy (did not review Flebogamma)

Donna Katz

Kevin Krudys (did not review Namenda XR or Flebogamma)

Wiley Chambers

Nisha Jain (Flebogamma review only)

Barbara Buch

Adrienne Hornatko-Munoz (Flebogamma review only)

PREA

10:50	NDA	21782/16 & 22285/18	Keppra XR & IV (levetiracetam) Assessment	XR - for adjunctive therapy in the treatment of partial onset seizures in patients ≥ 12 years of age with epilepsy IV - Adjunct therapy in patients with the following seizure types: 1) partial onset seizures in patients one month of age and older with epilepsy, 2) myoclonic seizures in patients 12 years of age and older with juvenile myoclonic epilepsy, and 3) primary generalized tonic-clonic seizures in patients 6 years of age and older with idiopathic generalized epilepsy
11:10	NDA	22525	Namenda XR (memantine) Assessment	Treatment of the core social impairment symptoms in subjects (6-12 years) with autism or autism spectrum disorder (ASD)
11:30	BLA	125077/296	Flebogamma Immune Globulin IV Assessment	Replacement therapy in pediatric patients with primary immunodeficiency diseases (PI)
	<i>NDA</i>	<i>21518</i>	<i>VESIcare (solefenacin succinate) Deferral Extension</i>	<i>Neurogenic Detrusor Overactivity</i>
	<i>NDA</i>	<i>21936</i>	<i>Spiriva (tiotropium) Full Waiver</i>	<i>COPD</i>
	<i>NDA</i>	<i>205060</i>	<i>Epanova (omega-3-carboxylic acids) Full Waiver</i>	<i>Adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia.</i>
	<i>NDA</i>	<i>204977</i>	<i>Omtryg (omega-3-acid ethyl esters)</i>	<i>Adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia.</i>

Keppra XR & IV Assessments

- NDAs 21782/16 & 22285/18 seeks review of Keppra XR & IV (levetiracetam) for **XR** - for adjunctive therapy in the treatment of partial onset seizures (POS) in patients ≥ 12 years of age with epilepsy and **IV** - Adjunct therapy in patients with the following seizure types: 1) partial onset seizures in patients one month of age and older with epilepsy, 2) myoclonic seizures in patients 12 years of age and older with juvenile myoclonic epilepsy, and 3) primary generalized tonic-clonic (PGTC) seizures in patients 6 years of age and older with idiopathic generalized epilepsy
- The applications have PDUFA goal dates of July 30, 2014 (IV) and August 4, 2014 (XR) respectively.
- *PeRC Recommendations:*
 - The PeRC agreed that the assessment for the IV formulation, which will be labeled down to 1 month of age for POS, 6 years of age for PGTC seizures and 12 years of age for myoclonic seizures, is complete
 - The Division clarified that the PREA PMRs for the XR product were issued prior the PeRC policy to require development of long-acting

formulations for younger patients. Therefore, this PREA requirement only required studies down to 12 years of age.

- The PeRC agreed with the Division's assessment and recommended that all available information be reviewed to extend the indication for POS to younger patients based on weight as appropriate. The PeRC also agreed that no further studies are necessary for the existing XR product because there are approved alternatives for treating patients with POS down to 1 month of age (e.g., the IR and IV formulations).

Namenda XR Assessment (WR Review)

- NDA 22525 seeks review of Namenda XR (memantine) for the treatment of the core social impairment symptoms in subjects (6-12 years) with autism or autism spectrum disorder (ASD)
- The application has a PDUFA goal date of January 8, 2015.
- The application triggers PREA as a new: active ingredient, indication, dosage form, dosing regimen, and route of administration.
- The Division summarized the studies performed under the WR. Two studies were performed and failed to demonstrate effectiveness of the product for social impairment symptoms. The Division noted that there was a large placebo effect and that the pre-specified treatment effect based on the SRS endpoint may not have been sufficiently large to detect a difference between placebo and treatment. The Division also noted a difference in treatment effect in U.S. and non U.S. patients.
- *PeRC Recommendations:*
 - The PeRC appreciates the Division's summary of the studies performed under the WR.

Flebogamma Immune Globulin IV Assessment

- BLA 125077/296 seeks review of Flebogamma (immune globulin) for replacement therapy in pediatric patients with primary immunodeficiency diseases (PI).
- *PeRC Recommendations:*
 - The PeRC agreed with the Division's review of the pediatric assessment. The Division clarified that the product demonstrated efficacy and should be indicated for use down to 2 years of age.
 - The PeRC will administratively waive studies less than 2 years of age and consider the PREA PMC fulfilled for patients 2 years of age and older.

VESIcare Deferral Extension

- NDA 21518 seeks review of VESIcare (solefenacin succinate) which is indicated for the treatment of Neurogenic Detrusor Overactivity(NDO).
- *PeRC Recommendations:*
 - The PeRC agreed with the deferral extension on the grounds that there was good cause for the delay in the completion of studies (slower than expected enrollment despite efforts to increase enrollment).

- The PeRC also notes for the record that deferral extensions granted for a PREA PMR should not be based solely on administrative changes to the date of completion of the same studies issued under a WR.

Spiriva Full Waiver

- NDA 21936 seeks review of Spiriva (tiotropium) for the treatment of COPD
- The application has a PDUFA goal date of January 8, 2015.
- The application triggers PREA as a new dosage form.
- *PeRC Recommendations:*
 - The PeRC agreed with the Division to grant a full waiver in pediatric patients because studies would be impossible or highly impractical due to the fact that the disease/condition does not occur in the pediatric population.

Epanova Full Waiver

- NDA 205060 seeks review of Epanova (omega-3-carboxylic acids) as adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia.
- The application has a PDUFA goal date of May 5, 2014.
- The application triggers PREA as a new active ingredient.
- *PeRC Recommendations:*
 - The PeRC did not formally review this PREA PMR because it was already issued.
 - The PeRC administrative staff has contacted the Division about the requirement to review all PREA PMRs prior to approval.

Omtryg Full Waiver

- NDA 204977 seeks review of Omtryg (omega-3-acid ethyl esters) as adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia.
- The application has a PDUFA goal date of November 30, 2013.
- The application triggers PREA as a new active ingredient.
- *PeRC Recommendations:*
 - The PeRC did not formally review this PREA PMR because it was already issued.
 - The PeRC administrative staff has contacted the Division about the requirement to review all PREA PMRs prior to approval.

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/s/

GEORGE E GREELEY
06/03/2014



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

ELECTRONIC CORRESPONDENCE

DATE: May 15, 2014

To: Ingeborg Arny-Cornejo, MD Sr. Associate Director Regulatory Affairs	From: Jessica Lee, PharmD Regulatory Project Manager
Company: Boehringer Ingelheim	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: 203-791-6262	Fax number: 301-796-9728
Phone number: 203-798-9988	Phone number: 301-796-3769

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NDA 21936

Dear Dr. Arny-Cornejo:

Your submission dated, March 24, 2014, to NDA 21936, is currently under review. We have the following request for information:

For Clinical Study 205.372 submit a detailed description for all of your primary efficacy datasets and the variables used in your efficacy analyses. Also provide all program code used for your primary efficacy analyses.

Submit responses to the NDA by Thursday, May 22, 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.

NDA 21936

Drafted by: KHamilton/May 14, 2014
JLee/May 14, 2014

Initialed by: LJafari/ May 15, 2014

Finalized by: JLee/May 15, 2014

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/s/

JESSICA K LEE
05/15/2014



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

ELECTRONIC CORRESPONDENCE

DATE: May 2, 2014

To: Ingeborg Arny-Cornejo, MD Sr. Associate Director Regulatory Affairs	From: Jessica Lee, PharmD Regulatory Project Manager
Company: Boehringer Ingelheim	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: 203-791-6262	Fax number: 301-796-9728
Phone number: 203-798-9988	Phone number: 301-796-3769

Subject: Information Request

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Dear Dr. Arny-Cornejo:

Your submission dated, March 24, 2014, to NDA 21936, is currently under review. We have the following request for information:

- 1) Provide two tables summarizing the pooled results from the 48-week exacerbation trials (205.254, 205.255, and 205.372) for all serious adverse events (1st table) and adverse events (2nd table). Use a format similar to table 15.3.2.3:2 (pg 374-379) from the clinical trial report from trial 205.452. Provide similar sets of tables for the 12-week bronchodilation trials (205.251 and 205.252).
- 2) For trial 205.452, provide a table summarizing overall and fatal MACE based on outcome events (MI, stroke, and TIA) broken down by components. Provide in a format similar to table 2.9.3 (pg 899) of the scs-supplement-study-report-body; or provide the location where this may be found.
- 3) In the document titled “BI trial 205.452 Embellished Clinical Narratives,” you state the following:

“A narrative template (see Drug Safety Manual, which is appended to the 205.452 clinical trial report [CTR] [U13-3560, Appendix 16.1.1.4.3]) was designed to capture all pertinent information to provide a summary of the subject’s clinical course for the following events, including selected categories of special interest (where 'all' refers to all serious and nonserious events in each category):

1. Fatal events
2. All strokes (and TIAs)
3. All myocardial infarctions (MI)
4. All cardiac arrhythmias
5. All events of syncope”

However, in section 5.2.2.1 of the protocol, neither cardiac arrhythmia nor syncope were included in the list of adverse events that were to be collected. Clarify how information on cardiac arrhythmias and syncope was collected.

- 4) On table 2.1.5.1.2:1 (pg 80) of the Summary of Clinical Safety, for the columns pertaining to trial 205.452, the “N” for the Tio R 5 treatment group reads “5713” and for Tio HH 18 it reads “5705”. This does not match the source data. A similar discrepancy is found on and 2.1.7.1.3:2 (pg 117). Please clarify.
- 5) During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments:
 - a. **Highlights:** There must be no white space between the product title and Initial U.S. Approval.

- b. **Full Prescribing Information (FPI)**: Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by May 23, 2014. The resubmitted labeling will be used for further labeling discussions.

Submit responses to points 1 to 4 to the NDA by Friday, May 9, 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.

NDA 21936

Drafted by: BLim/May 1, 2014
JLee/May 1, 2014

Initialed by: LJafari/May 2, 2014

Finalized by: JLee/May 2, 2014

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/s/

JESSICA K LEE
05/02/2014



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

ELECTRONIC CORRESPONDENCE

DATE: April 4, 2014

To: Ingeborg Arny-Cornejo, MD Sr. Associate Director Regulatory Affairs	From: Jessica Lee, PharmD Regulatory Project Manager
Company: Boehringer Ingelheim	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: 203-791-6262	Fax number: 301-796-9728
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NDA 21936

Dear Dr. Arny-Cornejo:

Your submission dated, March 24, 2014, to NDA 21936, is currently under review. We have the following request for information:

We seek clarification on the enrolled subjects for Study 0205-0372. In the 0205-0372-bimo.xpt file provided in your Application, it appears that the number of enrolled subjects reported for each treatment arm were the total number of entered subjects at a given site, rather than the number of subjects in the specific arm at the site. Provide a revised 0205-0372-bimo.xpt file, in which the number of enrolled (entered) subjects in each treatment arm, by site, are reported.

Submit a response to the NDA by Close of Business, Friday, April 11, 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.

NDA 21936

Drafted by: AOrencia/April 4, 2014
JLee/April 4, 2014

Initialed by: LJafari/April 4, 2014

Finalized by: JLee/April 4, 2014

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/s/

JESSICA K LEE
04/04/2014



NDA 21936

**ACKNOWLEDGE –
CLASS 2 RESUBMISSION**

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

Attention: Ingeborg Arny-Cornejo, MD
Sr. Associate Director
Regulatory Affairs

Dear Dr. Arny-Cornejo:

We acknowledge receipt on March 24, 2014, of your March 24, 2014, resubmission to your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Spiriva Respimat (tiotropium bromide) inhalation spray.

We consider this a complete, class 2 response to our September 16, 2008, action letter. Therefore, the user fee goal date is September 24, 2014.

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

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
04/04/2014



NDA 21936

**MEETING REQUEST-
WRITTEN RESPONSES**

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

Attention: Ingeborg Arny Cornejo, MD
Sr. Associate Director
Drug Regulatory Affairs

Dear Dr. Arny Cornejo:

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

We also refer to your submission dated February 26, 2013, containing a Type C meeting request. The purpose of the requested meeting was to discuss the proposed NDA resubmission for Spiriva Respimat.

Further reference is made to our Meeting Granted letter dated February 28, 2013, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your April 12, 2013 background package.

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:
Written Responses



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

WRITTEN RESPONSES

Meeting Type: C
Meeting Category: Guidance

Application Number: NDA 21936
Product Name: Spiriva Respimat
Indication: Chronic Obstructive Pulmonary Disease (COPD)
Sponsor/Applicant Name: Boehringer Ingelheim
Regulatory Pathway: 505(b)(1)

1.0 BACKGROUND

The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) took a Complete Response action on September 26, 2008, for NDA 21936, Spiriva Respimat. Boehringer Ingelheim submitted a Type C meeting request on February 26, 2013, for the purpose of discussing the resubmission of NDA 21936, Spiriva Respimat. The meeting was granted as Written Responses Only on February 28, 2013, with the goal date for providing the written responses by May 12, 2013.

Boehringer Ingelheim's background information and specific questions are italicized while FDA responses are in normal font.

2. QUESTIONS AND RESPONSES

2.1. Regulatory

Question 1:

Does the Division agree that there are no additional, outstanding information requests or deficiencies from the initial review of NDA 021936 that need to be addressed in our NDA resubmission?

FDA Response to Question 1:

It appears that you are addressing the clinical issues raised in the complete response. Whether these issues have been fully resolved will be a review issue.

Question 2:

Does the Division agree that in the case of separate NDAs for the indications of COPD and asthma, BI can cross-reference CMC data submitted to NDA 021936 in an NDA for SPIRIVA RESPIMAT in asthma?

FDA Response to Question 2:

Yes, we agree.

Question 3:

Does the Division agree that the proposed CMC cross-referencing would be accepted if NDA 021936 were still under review at the time of the asthma NDA submission?

FDA Response to Question 3:

Yes, we agree.

Question 4:

BI intends to submit a Label Update based on data from studies 205.452 and 205.458 for SPIRIVA HANDIHALER (NDA 021395) in close time-proximity to the SPIRIVA RESPIMAT resubmission (e.g. while SPIRIVA RESPIMAT for COPD is still under FDA review and evaluation). The label update will be based on these two studies directly comparing SPIRIVA RESPIMAT to SPIRIVA HANDIHALER.

Does the Division agree to this proposed approach including timelines?

FDA Response to Question 4:

Unless a safety issue is identified that warrants expeditious inclusion in the Spiriva HandiHaler label, we suggest that you wait until the action is complete on the Spiriva Respimat resubmission before submitting a supplement to the Spiriva HandiHaler NDA. Determination of what safety information is appropriate for the Spiriva HandiHaler label will be a review issue.

Question 5:

Based on the draft table of contents (Appendix 3) for the NDA resubmission, does the Division have any comments about the general organization and proposed content?

FDA Response to Question 5:

The general organization and content appear reasonable.

Question 6:

Based on the mock summaries, does the Division have any comments about the general organization and proposed content?

FDA Response to Question 6:

The general organization and content appear reasonable.

Question 7:

The following items have been provided with our initial NDA submission, dated November 16, 2007:

- 1.1.3 *User fee cover sheet: FDA form 3397*
- 1.12.14 *Environmental analysis*

We are not planning to resubmit or cross-reference these items within our NDA resubmission.

Does the FDA agree with this approach?

FDA Response to Question 7:

This approach is reasonable.

Question 8:

It is BI's intention not to resubmit Clinical studies previously submitted to the SPIRIVA RESPIMAT NDA 21936 or to the SPIRIVA HANDIHALER NDA 021395, and to provide cross-references to the previously submitted CTRs instead.

Does the FDA agree with this approach?

FDA Response to Question 8:

This approach appears reasonable.

Question 9:

BI provided draft labeling text within our initial NDA submission, dated November 16, 2007. Labeling comments from FDA were received on March 13 and April 24, 2008. BI responded to these information requests on June 20, 2008. No further information request was received thereafter. In FDA's Complete Response Letter it was stated that "We (FDA) reserve comment on the proposed labeling until the application is otherwise adequate. If you revise this labeling, your response must include updated content of labeling".

BI intends to harmonize the updated labeling text for SPIRIVA RESPIMAT whenever appropriate with the approved labeling texts for SPIRIVA HANDIHALER (current USPI approved March 2012) and COMBIVENT® RESPIMAT® (current USPI approved August 2012). This harmonization may result in the movement of some information for SPIRIVA RESPIMAT to a different section/subsection, divided into several subsections, etc. For ease of review we will provide the updated draft labeling in our NDA resubmission without track change mode (updated labeling of the NDA resubmission versus the previous version, dated June 20, 2008).

Does the FDA agree with this approach?

FDA Response to Question 9:

Yes, we agree.

Question 10:

In several sections of the proposed labeling, information from the approved SPIRIVA HANDIHALER (NDA 021395) and COMBIVENT RESPIMAT (NDA 21-747) labeling that is applicable to SPIRIVA RESPIMAT, will be provided verbatim. The annotated package insert for SPIRIVA RESPIMAT will identify the SPIRIVA HANDIHALER and COMBIVENT RESPIMAT package inserts as the references for this type of information.

Does the Division concur with this approach?

FDA Response to Question 10:

This approach is reasonable.

Question 11:

Section 6 of the USPI will describe the overall adverse reaction profile of the drug based on the entire tiotropium safety database (including clinical studies, published literature, post-marketing data and spontaneous reports) as described in the Core Company Data Sheet (CCDS) for SPIRIVA RESPIMAT and SPIRIVA HANDIHALER which lists the adverse drug reactions identified by the company. Only the adverse reactions listed in the CCDS will be included in the SPIRIVA RESPIMAT USPI. The frequencies of the adverse reactions (% patients) will be those observed in an integrated analysis of seven randomized, placebo-controlled, double-blind, parallel-group studies of at least 4 weeks treatment duration in which SPIRIVA RESPIMAT was studied in COPD (studies 205.251/252/254/255/372 and 1205.4/14). All adverse events from these studies will be included in the frequency estimation irrespective of whether the investigator considered the event to be causally related to drug exposure.

Does the Division concur with this approach?

FDA Response to Question 11:

Pending review of the safety data, this approach appears generally reasonable. Discussion of the specific contents of label section 6 is premature at this time.

Question 12:

In addition to the proposed bronchodilator indication, BI will provide information to support the proposed indication of reduction of COPD exacerbation. The primary support for the indication will come from study 205.372 (placebo controlled study). This study provides an independent data set demonstrating the reduction of exacerbations compared to placebo that is confirmed by the pooled data from studies 205.254 and 205.255. It is anticipated that study 205.452 will provide support for the SPIRIVA RESPIMAT exacerbation outcome.

BI plans to include quality of life information in the SPIRIVA RESPIMAT USPI. This information will be based on a pooled analysis of studies 205.254/255 included in the initial NDA submission and new data from study 205.372.

In section 14 of the USPI, BI will provide information from the new studies (study 205.452 fatal events, exacerbation and lung function data, study 205.372 exacerbation data, and study 205.458 PK data). The trial statistical analysis plan (TSAP) for study 205.452 can be found as [Appendix 9](#).

Does the Division have any comments to this proposed label strategy?

FDA Response to Question 12:

Pending review of trial data, your strategy is generally reasonable. Discussion of the specific contents of label section 14 is premature at this time. Note that inclusion of specific label

claims (e.g. quality of life, exacerbation, and mortality data) in section 14 will be a review issue.

Question 13:

This Background Information Package includes a mock summary for Module 2.7.1 (Appendix 4). This Clinical summary provides information on the new bioanalytical methodology (employed in trial 205.458) used for analyzing tiotropium compared to previously used methods, as well as device and dose information regarding SPIRIVA RESPIMAT. This section also includes a description of the planned comparisons (by means of ratios) of the exposure to tiotropium following inhalation from the RESPIMAT or HANDIHALER device based on pooled data (cross-over trials 205.458, 205.249, 205.250 and 205.291).

Does the Division agree with this approach and more specifically with the pooling approach for the PK data derived from various clinical studies provided in Module 2.7.1, Section 3 (“Comparison and analyses of results across studies”) ?

FDA Response to Question 13:

Your proposal seems acceptable. In addition, provide individual study report and analysis for the new PK study 205.458.

Clinical Pharmacology Studies

This Background Information Package includes a mock summary for Module 2.7.2 (Appendix 5). This Clinical summary summarizes the influence of external and internal factors on the pharmacokinetics of tiotropium using pooled data from various trials (trials 205.458, 205.249 and 205.250) using tiotropium RESPIMAT. The pharmacokinetics of tiotropium following inhalation via RESPIMAT are summarized as the basis for the USPI pharmacokinetic section. Pharmacokinetic data pertaining to the molecule, derived from trials using HANDIHALER or intravenous administration, will be referenced in the label.

Question 14:

Does the Division agree with this approach?

FDA Response to Question 14:

Your proposal seems acceptable.

Question 15:

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 (Appendix 5, section 3)?

FDA Response to Question 15:

Your proposal seems acceptable.

Question 16:

Module 2.7.3 and integrated analyses

This Background Information Package includes a mock summary for the SCE (Appendix 6). As will be explained in Section 1 of the Mock SCE, BI is proposing an integrated efficacy analysis in fulfillment of 21 CFR 314.50(d)(5)(v) in a format comparable to that used in the initial NDA submission:

- *Description of new study data in the context of the previously submitted studies in the SCE (Module 2.7.3)*
- *Individual CTRs of studies 205.372, 205.452 and 205.458 (Modules 5.3.5.1 and 5.3.4.2)*
- *Statistical analyses (Module 5.3.5.3)*

Since the NDA resubmission will be submitted as an eCTD, BI will make appropriate use of hyperlinking to ensure a seamless connection between Module 2.7.3 (SCE) and the respective tables and figures in the individual reports in Module 5.3.5.1/5.3.4.2 and the analyses in Module 5.3.5.3. Examples of efficacy displays and draft table content can be found as Appendix 10.

Does the FDA agree with this proposal?

FDA Response to Question 16:

This approach is reasonable.

Question 17:

Overall bronchodilator assessment

The summary of clinical efficacy (SCE) will focus on the comparison of the proposed dose for registration for SPIRIVA RESPIMAT (5 µg) versus placebo.

An SCE describing the studies 205.249, 205.250, 205.251, 205.252, 205.254 and 205.255 has already been submitted in the initial NDA submission, dated November 16, 2007. These studies were submitted primarily to support the bronchodilator outcomes. Bronchodilator data from study 205.372 will be added to show efficacy of SPIRIVA RESPIMAT irrespective of concomitant LABA use.

In order to investigate the comparability of lung function improvements between SPIRIVA RESPIMAT and SPIRIVA HANDIHALER, we plan to analyze the 205.452 bronchodilator data up to 120 weeks, and will provide this information for the USPI.

Does the FDA have any comments on this proposal?

FDA Response to Question 17:

We agree with your approach to provide comparative lung function data up to week 120 between Spiriva Respimat and Spiriva HandiHaler in your submission. However, inclusion in the USPI will be a review issue.

Question 18:

Second clinical deficiency (exacerbation indication)

The Division required an additional “adequate and well controlled study” to support the indication COPD exacerbation reduction. As previously noted, BI will submit an updated SCE presenting data from studies 205.372 and 205.452 alongside the pooled data from studies 205.254 and 205.255, to support the exacerbation indication. Study 205.372 will provide a primary dataset demonstrating a reduction of exacerbations compared to placebo. Confirmatory data will come from the pooled analysis of studies 205.254 and 205.255. Study 205.452 (active controlled study) will provide additional supportive evidence for the exacerbation indication, as well as long-term effects in comparison to SPIRIVA HANDIHALER. BI considers that the totality of this information will allow a very robust assessment of the tiotropium RESPIMAT exacerbations outcomes. Further details of the planned analyses will be presented in the Mock SCE.

The results of the pooled studies (205.254/255) and study 205.372 will be provided separately, as studies 205.254/255 excluded concomitant LABA use, while 205.372 allowed concomitant LABA use.

Does the Division have any comments on this proposal?

FDA Response to Question 18:

This approach is reasonable.

Question 19:

Module 2.7.4 and integrated analyses

This Background Information Package includes a mock summary for the SCS ([Appendix 7](#)). As will be explained in Section 1 of the Mock SCS, BI is proposing an integrated safety analysis in fulfillment of 21 CFR 314.50(d)(5)(v) in a format comparable to that used for the initial NDA submission:

- *Description of new study data in the context of the previously submitted studies in the SCS (Module 2.7.4)*
- *Individual CTRs of studies 205.372, 205.452, 1205.4 and 1205.14 (Module 5.3.5.1)*
- *Integrated safety analyses including sub-group analyses (Module 5.3.5.3, and summarized in Module 2.7.4)*

Since the NDA resubmission will be provided as an eCTD, BI will make appropriate use of hyperlinking to ensure a seamless connection between Module 2.7.4 (SCS) and the respective tables and figures in the individual reports in Module 5.3.5.1 and the combined reports in Module 5.3.5.3. Examples of safety displays and draft table content can be found as [Appendix 11](#) and [Appendix 12](#) respectively.

Does the FDA agree with this proposal?

FDA Response to Question 19:

This approach is reasonable.

Question 20:

Does the Division have any comments on the proposed scope/organization of the overall safety strategy (including the clinical deficiencies of imbalanced fatal outcomes and stroke noted in the Complete Response letter)?

FDA Response to Question 20:

In general, the proposed organization of your safety strategy seems reasonable. In order to see combined occurrence rates of medically similar adverse events, we recommend that you collapse MedDRA preferred terms for adverse events of interest (e.g. stroke, myocardial infarction, atrial fibrillation, etc.) in addition to providing preferred terms. Also include narratives for AEs leading to discontinuation for trial 205.372.

Since your program relies in part on safety data from the UPLIFT trial, it will be important that your submission addresses key issues that have been raised in the published literature regarding UPLIFT and if any of these issues also apply to Trial 205.452. For example, concerns regarding exclusion of patients with moderate to severe renal impairment, a history of recent MI, unstable or life threatening cardiac arrhythmia or admission for heart failure were raised for UPLIFT (BMJ 2012; 345:e7390). We acknowledge that you have previously addressed many of the issues raised in the literature for UPLIFT [NDA 21-395, submission dated August 16, 2011], and recommend that you summarize key issues for ease of review, also correlating how these issues may relate to the current Complete Response submission. In addition, given the concerns raised regarding the drop off in vital status data 30 days post-treatment (NEJM 2009; 360: 185-187) and the difference in collection of vital status information based upon the definition of a completed patient in UPLIFT, ensure that your submission provides clear definitions of the different mortality datasets for Trial 205.452 and an explanation for any significant drop off in vital status data, if applicable.

Question 21:

Subgroup selection

The primary safety endpoint (time to death) will be presented for the following subgroups:

- *Age: <60 years, 60 to <70 years, >=70 years*
- *Race subgroups: white, black, Asian, other/missing*
- *Gender: male, female*
- *BMI: normal, underweight, overweight*
- *Severity stage at baseline based on post-bronchodilator FEV1: GOLD stages I+II, III, IV*
- *Cardiac arrhythmia history: yes, no*
- *Smoking status at baseline: current smoker, ex-smoker*
- *LABA use at baseline: yes, no*
- *ICS use at baseline: yes, no*
- *Country USA: yes, no*

Does the FDA agree with this currently proposed list of subgroups?

FDA Response to Question 21:

Include sub-group analysis of patients with a cardiac history (yes/no). The proposed sub-groups are otherwise acceptable pending review of safety data.

Question 22:

Safety Update

The BI integrated safety database for tiotropium RESPIMAT (RESPIMAT 7-study integrated placebo-controlled safety database) together with Study 205.452 will be used to provide a complete safety update. The 28-study "HH integrated placebo-controlled safety database" will be used for comparison.

BI tiotropium studies qualify for inclusion in the integrated safety database for SPIRIVA RESPIMAT and SPIRIVA HANDIHALER respectively based on the following criteria:

- *treatment with SPIRIVA RESPIMAT or SPIRIVA HANDIHALER*
- *COPD indication*
- *randomised, double-blind, placebo-controlled, parallel group design*
- *treatment duration of at least 4 weeks*

BI will base the safety evaluation on clinical data obtained with tiotropium RESPIMAT in the COPD indication rather than including data obtained in the asthma or cystic fibrosis programs, due to the substantial safety database available for tiotropium in COPD and the different patient characteristics in these indications. Clinical studies of tiotropium RESPIMAT in these other indications will be evaluated within their respective clinical development programs. BI is not planning to submit an NDA or sNDA for SPIRIVA RESPIMAT treatment of airflow obstruction associated with cystic fibrosis.

The NDA resubmission will include a new summary of clinical safety (Module 2.7.4), which will focus on new clinical study data (tiotropium RESPIMAT in COPD), put into the context of already submitted data. Additionally, post-marketing experience for SPIRIVA RESPIMAT will be included. BI will be submitting within the NDA resubmission individual CTRs (specifically 205.372, 205.452), and new integrated safety analyses including subgroup analyses (Module 5.3.5.3), summarized in the SCS. As the SCS will provide an integrated data presentation of all available safety data, a separate stand-alone formal safety update report will not be provided with the NDA resubmission.

Does the described scope of information and analysis plan fulfill the requirements of a complete safety update in accordance with 21 CFR 314.50(d)(5)(vi)(b) and as referenced in the Complete Response letter?

FDA Response to Question 22:

See response to question 20 and 21.

Question 23:

In the initial NDA, case report tabulations in electronic format were provided for ten SPIRIVA RESPIMAT clinical trials, two Phase I clinical studies (205.112 and 205.138), two

Phase II clinical studies (205.127 and 205.248) and six Phase III clinical studies (205.249, 205.250, 205.251, 205.252, 205.254 and 205.255).

BI is not proposing to resubmit these data. Does the FDA have any comment on this proposal?

FDA Response to Question 23:

This is reasonable.

Question 24:

In the initial NDA analysis data sets (BI format) were provided for the six Phase III clinical studies (205.249, 205.250, 205.251, 205.252, 205.254 and 205.255).

BI is not proposing to resubmit these data. Does the FDA have any comment on this proposal?

FDA Response to Question 24:

This is acceptable.

Question 25:

Details of the proposed data sets (raw data sets, SDTM and analysis data sets), documentation and SAS programs for the resubmission can be found in [Appendix 13](#).

Does the Division have any comments on the data set proposals?

FDA Response to Question 25:

This is acceptable.

Question 26:

Does FDA have any comments regarding BI's proposal to provide a complete Module 3 in the NDA Resubmission, plus a Reviewer's Guide that describes the changes in the CMC documentation?

FDA Response to Question 26:

Due to the extended time that has passed since the complete response action, we request the following to ensure the efficiency of our evaluation:

- The reviewer guide should clearly summarize the changes and new and updated information so that re-evaluation of previously submitted information is not likely to occur, or only occurs when necessary.
- Include hyperlinks in the reviewer guide so that it is easy to locate and review new and updated information and changes.
- It is indicated in appendix 8 that some sections of module 3 are “re-organized.” It should be easy for the reviewer to determine and locate what information has changed or is new or updated (e.g., the text may be flagged or highlighted in some way, such as with the use of italics or different color fonts) and needs evaluation in these re-organized sections, without having to compare the resubmission module 3 to the previous module 3 in place at the time of the CR action.

- On p. 852 of 954 you state that newly added information will include “**information requested by FDA** during review of the original SPIRIVA RESPIMAT NDA, and during the review from the COMBIVENT RESPIMAT NDA.” One example is listed on p. 856, where you state that “As requested by FDA during the NDA review, the aerodynamic particle size distribution groupings (ACI and Laser) were modified by splitting Group 1 into two Groups 1a (i.e., Mouthpiece-adapter, SIP and Stage 0) and Group 1b (Stages 1 and 2).” It is unclear why this needs to be highlighted in the resubmission if the information had been previously submitted in the first review cycle in response to our request. The information highlighted in the reviewer guide should be **limited to** new, updated, or changed information, not what had been previously submitted and evaluated.
- Nevertheless, it is acknowledged that some changes (if deemed significant) may still require a re-evaluation of data submitted previously relative to new data, to assess the impact on the drug product.

Question 27:

FDA’s complete response letter of September 16, 2008 had no CMC deficiency comments to address in the resubmission of NDA 021936. However, there is a need for updates to the CMC documentation (as outlined in [Appendix 8](#)) to assure compliance with changes that have occurred in the intervening time since the issuance of FDA’s complete response letter.

In the SPIRIVA RESPIMAT NDA 021936 resubmission, BI intends to provide a complete replacement of Module 3 with updated CMC documentation. The NDA resubmission will be in eCTD format, and therefore this replacement of Module 3 will provide to both FDA and BI a complete electronic baseline for the CMC documentation supporting SPIRIVA RESPIMAT for the COPD indication. The structure of the documents will be consistent with that of the COMBIVENT RESPIMAT and Olodaterol RESPIMAT NDAs (021747 and 203108) and will capture, where applicable, FDA requested information from these NDAs.

To support the review of the SPIRIVA RESPIMAT NDA resubmission, an FDA reviewer’s guide will be provided in Module 1. This document will detail the CMC document changes.

Additionally, the NDA resubmission will include a Quality Overall Summary document (Module 2.3).

Does FDA agree with BI’s proposal, that the stability performance data generated using the 28 actuation size of Olodaterol RESPIMAT (NDA 203108) supports the 28 actuation size of SPIRIVA RESPIMAT (NDA 021936), and that no stability data specifically for SPIRIVA RESPIMAT using the 28 actuation RESPIMAT device is required.

FDA Response to Question 27:

Yes, we agree.

Question 28:

BI intends to have RESPIMAT inhalers that provide 28 actuations (14 doses) of the drug

product. As explained in Appendix 8 (sections 3.2.P.1 and 3.2.P.8.1), these inhalers are identical to the 60 actuation inhaler except that the locking mechanism will lock the device after approximately 28 actuations instead of 60 actuations. The 28 actuation size is intended to be used in the hospital setting and as physician samples. BI recently submitted accelerated stability (6 months at 40°C/75% r.h.) data for the 28 actuation RESPIMAT® size as suggested by FDA in their correspondence of September 25, 2008 (IND 76397) to the Olodaterol RESPIMAT NDA (203108). In that correspondence, FDA agreed that BI's proposed data to be provided in the Olodaterol RESPIMAT NDA (203108) would be evaluated in support of the proposal to eliminate post approval annual batch stability testing for the 28 actuation RESPIMAT size.

Since the RESPIMAT inhaler is the same for all RESPIMAT drug products (only differing in the set up of the locking mechanism), and the RESPIMAT inhaler controls the delivered volume and aerodynamic droplet size distribution, no additional stability data for the 28 actuation RESPIMAT size is proposed for the SPIRIVA RESPIMAT NDA resubmission.

Does FDA agree that no additional executed batch records need to be submitted?

FDA Response to Question 28:

Yes, we agree.

Question 29:

Does the FDA agree that the scope, content and format of the NDA resubmission as described throughout the documents contained herein constitute a complete response to issues raised in FDA's Complete Response Letter, dated September 16, 2008?

FDA Response to Question 29:

See response to question 1.

Question 30:

Will the scope of information provided in this NDA resubmission be reviewed within the PDUFA-defined 6-month goal?

FDA Response to Question 30:

Assuming that sufficient information is submitted to permit adequate review of the deficiencies listed in the Complete Response Letter, we intend to review this re-submission within the 6-month goal. We encourage you to submit the final clinical trial reports and data sets from trials 205.452 and 205.372 to the IND as soon as they become available, ideally in advance of the NDA resubmission. We note that your IND 65,127 submissions of the 205.372 clinical trial report dated June 11, 2009, and October 8, 2009, did not contain data sets.

Question 31:

At the time of submission of NDA 021936 in 2007, the Division indicated that BI could expect the NDA to come before the Pulmonary-Allergy Drug Advisory Committee (PADAC). Can the Division comment on the likelihood of this NDA coming to a PADAC including anticipated time-lines?

FDA Response to Question 31:

Given the safety issues raised in the original submission, it is likely that this resubmission will go to PADAC prior to the action date.

3.0

PREA REQUIREMENTS

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit a Pediatric Study Plan (PSP) within 60 days of an End-of-Phase 2 (EOP2) meeting held on or after November 6, 2012. If an EOP2 meeting occurred prior to November 6, 2012 or an EOP2 meeting will not occur, then:

- if your marketing application is expected to be submitted prior to January 5, 2014, you may either submit a PSP 210 days prior to submitting your application or you may submit a pediatric plan with your application as was required under the Food and Drug Administration Amendments Act (FDAAA).
- if your marketing application is expected to be submitted on or after January 5, 2014, the PSP should be submitted as early as possible and at a time agreed upon by you and FDA. We strongly encourage you to submit a PSP prior to the initiation of Phase 3 studies. In any case, the PSP must be submitted no later than 210 days prior to the submission of your application.

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. For additional guidance on submission of the PSP, including a PSP Template, please refer to:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm> . In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov.

PRESCRIBING INFORMATION

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57. In particular, please note the following formatting requirements:

- Each summarized statement in the Highlights (HL) must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
- The section headings and subheadings (including title of the Boxed Warning) in the Table of Contents must match the headings and subheadings in the FPI.

- The preferred presentation for cross-references in the in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, "[see *Warnings and Precautions (5.2)*]".

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

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
05/10/2013



NDA 21936

**MEETING REQUEST GRANTED
WRITTEN RESPONSES ONLY**

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

Attention: Ingeborg Army Cornejo, MD
Sr. Associate Director
Drug Regulatory Affairs

Dear Dr. Army-Cornejo:

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

We also refer to your February 26, 2013, correspondence requesting a meeting to discuss the proposed NDA resubmission for Spiriva Respimat. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a Type C meeting.

We have determined that written responses to your questions would be the most appropriate means for responding to the meeting request. Therefore, a meeting will not be scheduled. Our goal date for providing our written responses is May 12, 2013.

Submit background information (three paper copies or one electronic copy to the application and 15 paper desk copies to the RPM) as soon as possible but no later than 1 month prior to our goal date for sending written responses (as stated above) for our review and response. If the materials presented in the background package are inadequate to answer the questions or if we do not receive the package by April 12, 2013, we may cancel the agreement to provide written responses. If we cancel the agreement to provide written responses, a new meeting request will be required.

Submit 15 desk copies to the following address:

Jessica K. Lee, PharmD
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 3385
10903 New Hampshire Avenue
Silver Spring, Maryland

*Use zip code **20903** if shipping via United States Postal Service (USPS).*

*Use zip code **20993** if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).*

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

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/s/

JESSICA K LEE
02/28/2013

MEMORANDUM

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

DATE: July 31, 2008

TO: Memo to the File of NDA 21936

FROM: Miranda Raggio, RN, BSN, MA, Regulatory Project Manager

SUBJECT: **Telephone Conversation**
NDA 21-936,

On July 31, 2008, at 10am, a telephone call was placed to Jeff Snyder, Executive Director, Office of Regulatory Affairs, Boehringer Ingelheim (BI) Pharmaceuticals. Attending from BI were also Eben Rubin, M.D. and Demetri Pavia, M.D. In attendance from the FDA, in addition to myself, were Drs. Sally Seymour and Theresa Michele. In keeping with GRMP guidelines the purpose of the meeting was to inform BI of our current plans related to the NDA 21936 submission (currently under review) with regards to labeling negotiations.

Dr. Seymour identified the following review issues:

1. Mortality imbalance in the one year Phase 3 trial
2. HandiHaler tiotropium stroke issue-outstanding safety issue
3. Exacerbation claim-we will only consider one of BI's studies for efficacy as support of the exacerbation claim; BI will need to replicate findings for a labeling claim.

Dr. Seymour informed Jeff Snyder that the Division plans to take an unfavorable action; therefore, there will be no labeling discussions related to NDA 21-936. Dr. Seymour also told Jeff that additional data to resolve the safety signal issues would be required, and if BI wished to pursue the exacerbation claim, that more supporting data for this claim would be necessary.

Jeff was informed that an Advisory Committee regarding these issues would most likely be convened in the future, and that the action letter will detail our specific issues of concern and state what actions need to be taken to resolve these issues.

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/s/

Miranda Raggio
8/4/2008 05:08:44 PM
CSO



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

FACSIMILE CORRESPONDENCE

Date: August 4, 2008

To: Jeffrey R. Snyder/Walter Robak

Company: Boehringer Ingelheim

Phone: 203-778-7727

Fax: 203-837-4928

From: Miranda Raggio, RN, BSN, MA
Regulatory Health Project Manager
Division of Pulmonary and Allergy Products

Phone: 301-796-2109

Subject: NDA 21-936 CMC Information Request

of Pages: 3

Comments: Please call with any questions. Thanks, miranda

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(301) 796-2109. Thank you.**

NDA 21-936

We are currently reviewing your NDA dated November 16, 2007, received November 16, 2007, for SPIRIVA Respimat. Provide the following information expeditiously.

- 1. Please clarify your commitment to reevaluate the drug product specifications after producing at least ten commercial batches by indicating that you will collect data from both Aerodynamic Particle Size Distribution methods, employing the Andersen Cascade Impactor and the Laser Diffraction methods. This is in addition to collecting data pertaining to the remainder of the specifications.*
- 2. Please prepare to submit at our request updated specifications to the application, including all changes agreed to in the course of our review of this NDA, including your future response to our Information Request sent to you on July 22, 2008.*

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

NDA 21-936

Drafted by: Miranda Raggio/July 31, 2008

Initialed by: Sandy Barnes/August 4, 2008
Alan Schroeder/August 4, 2008
Ali Al-Hakim/August 4, 2008

Finalized by: Miranda Raggio/August 4, 2008

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/s/

Miranda Raggio
8/4/2008 12:02:35 PM
CSO

Miranda Raggio
8/4/2008 12:02:57 PM
CSO



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

FACSIMILE CORRESPONDENCE

Date: July 22, 2008

To: Jeffrey R. Snyder

Company: Boehringer Ingelheim

Phone: 203-778-7727

Fax: 203-837-4928

From: Miranda Raggio, RN, BSN, MA
Regulatory Health Project Manager
Division of Pulmonary and Allergy Products

Phone: 301-796-2109

Subject: NDA 21-936 CMC Information Request/APSD

of Pages: 3

Comments: Please call with any questions. Thanks, miranda

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NDA 21-936

We are currently reviewing your NDA dated November 16, 2007, received November 16, 2007, for SPIRIVA Respimat. Provide the following information pertaining to the laser diffraction method (#20209) for aerodynamic particle size distribution (APSD):

1. Reference is made to your responses to our comments 13a and 13b in your April 18, 2008, amendment. Provide representative graphical stability data of the mean values of three drug product units to facilitate evaluation of the new proposed mean specifications for the groupings 1a and 1b.
2. Propose a lower limit to the acceptance criteria for grouping 3 for individual inhaler units, based on the data on page 18 of your amendment dated April 18, 2008 in response to our March 26, 2008 IR letter.

Please submit your response by COB on Monday, July 28, 2008.

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

NDA 21-936

Drafted by: Miranda Raggio/July 21, 2008

Initialed by: Sandy Barnes/July 21, 2008

Alan Schroeder/July 21, 2008

Ali Al-Hakim/July 21, 2008

Finalized by: Miranda Raggio/July 22, 2008

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/s/

Miranda Raggio
7/22/2008 09:39:47 AM
CSO

Miranda Raggio
7/22/2008 09:40:18 AM
CSO



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

FACSIMILE CORRESPONDENCE

Date: July 18, 2008

To: Jeffrey R. Snyder

Company: Boehringer Ingelheim

Phone: 203-778-7727

Fax: 203-837-4928

From: Miranda Raggio, RN, BSN, MA
Regulatory Health Project Manager
Division of Pulmonary and Allergy Products

Phone: 301-796-2109

Subject: NDA 21-936 CMC (laser diffraction method) clarification
Information Request

of Pages: 3

Comments: Please call with any questions. Thanks, miranda

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NDA 21-936

We are currently reviewing your NDA dated November 16, 2007, received November 16, 2007, for SPIRIVA Respimat. Please refer to comment #3 of the CMC related information request (IR) fax sent to you by the Division on May 27, 2008, and your response in the amendment submitted June 10, 2008.

Provide the following information pertaining to the laser diffraction method (#20209) for aerodynamic particle size distribution (APSD):

- 1) Explain the reason for averaging four runs at the beginning and four runs at the end of the inhaler life to generate a "single set" of APSD data, rather than averaging single runs at beginning and end of the inhaler life.*
- 2) Comment on individual run variability with this method.*

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

NDA 21-936

Drafted by: Miranda Raggio/July 16, 2008
Initialed by: Sandy Barnes/July July 17, 2008
Alan Schroeder/July 18, 2008
Ali Al-Hakim/July 18, 2008
Finalized by: Miranda Raggio/July 18, 2008

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/s/

Miranda Raggio
7/18/2008 10:22:06 AM
CSO

Miranda Raggio
7/18/2008 10:22:36 AM
CSO



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

FACSIMILE CORRESPONDENCE

Date: July 15, 2008

To: Jeffrey R. Snyder

Company: Boehringer Ingelheim

Phone: 203-778-7727

Fax: 203-837-4928

From: Miranda Raggio, RN, BSN, MA
Regulatory Health Project Manager
Division of Pulmonary and Allergy Products

Phone: 301-796-2109

Subject: NDA 21-936 Mortality/Covariates Information Request

of Pages: 3

Comments: Please call with any questions. Thanks, miranda

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(301) 796-2109. Thank you.**

We are currently reviewing your NDA dated November 16, 2007, received November 16, 2007, for SPIRIVA Respimat. Provide the following information for utilization in the review process of your application by close of business on July 17, 2008, for item #1, and by close of business on July 22, 2008, for items #2 and #3.

- 1) Provide exploratory statistical analyses examining the impact of the following covariates on mortality occurring in connection with studies 254 and 255: gender, age, race, FEV1 at baseline, cardiac history (i.e., presence or absence of coronary artery disease and presence or absence of arrhythmia), smoking history (i.e., pack years and active smoker versus not), country, and any other covariates you believe may further the understanding of the type of patient who is at risk for death. Include in the analyses both deaths reported during the original conduct of the studies as well as those collected retrospectively.
 - a) Provide results of such methods as Cox regression modeling investigating both the main effects for the covariates as well as the interactions of the covariates with treatment.
 - b) As the Cox modeling may not be adequate due to the low number of events, also provide analyses of mortality sub grouped by each of the covariates utilizing the same statistical methods as in your previous analysis of death in these studies (i.e., as in the safety update for NDA21936 dated March 18, 2008).
- 2) Provide analysis data sets used to create the analyses in #1 above.
- 3) In a May 7, 2008, response to FDA request for information, you provided data for COPD exacerbations for the 5mcg tiotropium Respimat group in Studies 205.254 and 205.255. Provide the same information for the 10mcg tiotropium Respimat group.

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

NDA 21-936

Drafted by: Miranda Raggio/July 15, 2008
Initialed by: Sandy Barnes/July 15, 2008
Ruthie Davi/July 15, 2008
Tom Permutt/July 15, 2008
Terri Michele/July 15, 2008
Sally Seymour, July 15, 2008
Finalized by: Miranda Raggio/July 15, 2008

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/s/

Miranda Raggio
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CSO

Miranda Raggio
7/15/2008 03:42:37 PM
CSO



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

FACSIMILE CORRESPONDENCE

Date: July 8, 2008

To: Jeffrey R. Snyder

Company: Boehringer Ingelheim

Fax: 203-778-7727

Phone: 203-837-4928

From: Miranda Raggio, RN, BSN, MA
Regulatory Health Project Manager
Division of Pulmonary and Allergy Products

Phone: 301-796-2109

Subject: NDA 21-936 Microbiology Information Request

of Pages: 4

Comments: Please call with any questions. Thanks, miranda

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(301) 796-2109. Thank you.**

We are currently reviewing your NDA dated November 16, 2007, received November 16, 2007, for SPIRIVA Respimat. We request that you provide the following information for utilization in the review process of your application by close of business on July 25, 2008.

1. Regarding container-closure integrity testing:

- a. Provide the size of needle used to create positive controls for the study (units with compromised container-closure integrity).
- b. State if the bacterial suspension count was verified following the challenge.
- c. Provide the growth medium used to incubate the membranes.
- d. State how long test units were incubated?

2. Regarding the preservative effectiveness test:

- a. Provide a summary of the counts obtained for (b) (4)
- b. Provide a summary of the media growth promotion results.

3. Regarding the environmental monitoring program:

- a. Provide a list and/or diagram of all locations monitored in the aseptic area.
- b. Provide the alert and action levels for the presence of bacterial endotoxins in Water for Injection.

4. Regarding drug solution (b) (4):

(b) (4)

5. Describe the re-qualification program (e.g., number and types of runs, frequency) (b) (4).

6. Regarding sterilization (b) (4), provide the following:

- a. A description of the microbiological methods (growth medium, incubation conditions) used [REDACTED] ^{(b) (4)}
[REDACTED]
 - b. A description and/or diagram of thermocouple and biological indicator placement in each load configuration (containers and caps) during the validation studies.
 - c. A data summary of the heat distribution mapping studies performed.
 - d. A description of the re-qualification program (e.g., number and type of runs, frequency).
 - e. The program for monitoring the stability of packaging and the integrity of the container-closure system barrier [REDACTED] ^{(b) (4)} over the shelf-life or until use.
7. It is stated that one media fill run is performed semi-annually. However, it appears from the data provided (July 2005 and October 2006) that media fills are performed annually. Provide a summary of the three most recent media fills and include the following information:
- a. Number of units filled, number of units inspected, number of units rejected (with justification), number of units incubated, and number of contaminated units.
 - b. A summary of the growth promotion results for each media fill.
 - c. A summary of the environmental monitoring results for each media fill.
 - d. Fill duration for each media fill. State if media fill runs simulated the [REDACTED] ^{(b) (4)} solution holding time.
 - e. A list of interventions performed in each media fill run.
8. Describe how product is disposed of before and after a failed media fill (e.g. investigation and reviews performed).
9. Provide a data summary of the bacteriostasis/fungistasis study for the product that demonstrates method suitability for the sterility test.

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

NDA 21-936

Drafted by Miranda Raggio/July 7, 2008

Initialed by Sandy Barnes/July 8, 2008

Alan Schroeder/July 8, 2008

Ali Al-Hakim/July 8, 2008

James McVey/

Finalized by Miranda Raggio/

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/s/

Miranda Raggio
7/8/2008 04:17:45 PM
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Office of New Drugs
Office of Drug Evaluation II**

FACSIMILE CORRESPONDENCE

Date: July 7, 2008

To: Jeffrey R. Snyder

Company: Boehringer Ingelheim

Phone: 203-778-7727

Fax: 203-837-4928

From: Miranda Raggio, RN, BSN, MA
Regulatory Health Project Manager
Division of Pulmonary and Allergy Products

Phone: 301-796-2109

Subject: NDA 21-936 STATS Information Request

of Pages: 3

Comments: Please call with any questions. Thanks, miranda

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(301) 796-2109. Thank you.**

NDA 21-936

We are currently reviewing your NDA dated November 16, 2007, received November 16, 2007, for SPIRIVA Respimat. Provide the following information for utilization in the review process of your application by close of business on Thursday, July 10, 2008.

Provide statistical analyses of all deaths occurring in connection with studies 205.254 and 205.255. Include in the analyses both deaths reported during the original conduct of the studies as well as those collected retrospectively. Report point estimates and 95% confidence intervals for the relative risk and excess incidence of death with each of the Spiriva Respimat treatment groups relative to placebo utilizing the same statistical methods as in your previous analysis of death in these studies (i.e., IND65127, serial 0126 dated May 31, 2006, response to FDA request #2). Present these results for each study individually as well as pooled.

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

NDA 21-936

Drafted by: Miranda Raggio/July 7, 2008

Initialed by: Sandy Barnes/July 7, 2008

Ruthie Davi/July 7, 2008

Qian Li/July 7, 2008

Finalized by: Miranda Raggio/July 7, 2008

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/s/

Miranda Raggio
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Office of New Drugs
Office of Drug Evaluation II**

FACSIMILE CORRESPONDENCE

Date: Jun 19, 2008

To: Jeffrey R. Snyder

Company: Boehringer Ingelheim

Phone: 203-778-7727

Fax: 203-837-4928

From: Miranda Raggio, RN, BSN, MA
Regulatory Health Project Manager
Division of Pulmonary and Allergy Products

Phone: 301-796-2109

Subject: NDA 21-936 CMC Information Request

of Pages: 3

Comments: Please call with any questions. Thanks, miranda

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(301) 796-2109. Thank you.**

NDA 21-936

We are currently reviewing your NDA dated November 16, 2007, received November 16, 2007, for SPIRIVA Respimat. We request that you provide the following information for utilization in the review process of your application by close of business on June 24, 2008.

Indicate if you were aware of the monomers and other raw materials used in manufacture [REDACTED] (b) (4) [REDACTED] prior to performing your extractable studies for the [REDACTED] (b) (4) [REDACTED] components of the Respimat and for the leachable studies of the drug product. If so, please indicate the target compounds for your extractable and leachable studies.

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

NDA 21-936

Drafted by: Miranda Raggio/June 15, 2008

Initialed by: Sandy Barnes/June 17, 2008

Alan Schroeder/June 19, 2008

Ali Al-Hakim/June 19, 2008

Finalized by: Miranda Raggio/June 19, 2008

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/s/

Miranda Raggio
6/18/2008 01:51:01 PM
CSO

Miranda Raggio
6/18/2008 01:51:22 PM
CSO



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

FACSIMILE CORRESPONDENCE

Date: May 27, 2008

To: Jeffrey R. Snyder

Company: Boehringer Ingelheim

Phone: 203-778-7727

Fax: 203-837-4928

From: Miranda Raggio, RN, BSN, MA
Regulatory Health Project Manager
Division of Pulmonary and Allergy Products

Phone: 301-796-2109

Subject: NDA 21-936 CMC Information Request

of Pages: 3

Comments: Please call with any questions. Thanks, miranda

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We are currently reviewing your NDA dated November 16, 2007, received November 16, 2007, for SPIRIVA Respimat. Provide the following information by close of business on June 10, 2008 for utilization in the review process of your application.

1. Provide an agreement stating that the analytical procedure for aerodynamic particle size distribution (APSD-LD) including the instrument, instrumental attachments, software, and procedure will not be changed after product approval, except with full validation and comparative data in a supplement to the NDA.
2. Clarify the appropriate values for all of the adjustable parameters, including physical parameters, instrumental settings, software settings required to use the APSD-LD method reproducibly.
3. Clarify the treatment of data (b) (4) for a single APSD-LD analysis (“run”) to yield a single set of particle size distribution data.
4. As the US Agent for Boehringer Ingelheim GmbH & CO. KG you have provided in Module 1 a letter of authorization (LOA) for DMF 18135 for the drug substance, dated March 29, 2007. , This LOA only pertains to the inhalation powder grade and specifically excludes the inhalation solution grade. Provide the appropriate LOA for this NDA.

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

NDA 21-936

Drafted by Miranda Raggio/May 23, 2008

Initialed by Sandy Barnes/May 23, 2008

Alan Schroeder/May 23, 2008

Ali Al-Hakim/May 27, 2008

Finalized by Miranda Raggio/May 23, 2008

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/s/

Miranda Raggio
5/27/2008 03:12:59 PM
CSO

Miranda Raggio
5/27/2008 03:13:38 PM
CSO

MEMORANDUM

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

DATE: May 8, 2008
TO: The File of NDA 21-936
FROM: Miranda Raggio, RMP, DPAP (570)
SUBJECT: **Clarification email to Jeff Snyder**
NDA 21-936,

Jeff Snyder, Regulatory Affairs for Boehringer Ingelheim, sent me an email on May 7, 2008, requesting clarifications on several points in an information request sent to BI on April 24, 2008. We responded via email on May 8, 2008. The original email, as well as our response, is found below:

Dear Miranda:

We will be providing a partial request to the clinical elements of the IR you faxed me on 24 April. However, the second clinical request has us a little stymied and we would appreciate it if you could take a look at the comments below and provide us some clarification. Please note that these comments will also be part of the formal response we are preparing for a 6 May 08 submission that addresses request 1.

2. Provide a subgroup analysis of the primary endpoint for protocols 205.254 and 205.255. Sort data by country/region.

- There are 4 primary endpoints for studies 205.254/255: are all 4 the subject of this request?
- Should the subgroup analyses be based on the pooled studies (otherwise the subgroups get really small)?
- The combined report for 205.254/255 (U05-2249) contains hypothesis tests (trough FEV1, SGRQ and TDI) for heterogeneity of treatment effect among the countries (20 countries). None of these tests suggested heterogeneity.
- The primary endpoints are not powered for sub-group analyses by country. Would a sub-group analysis by region where countries are split into two regions address your concerns? The table below shows the number of patients treated in each study in each country. Can you tell us which country you would like in each region?

	Trial number		
	205.254	205.255	Total

Number of patients	983(100.0)	1007(100.0)	1990(100.0)
Country [N (%)]			
Austria	0 (0.0)	60 (6.0)	60 (3.0)
Australia	45 (4.6)	34 (3.4)	79 (4.0)
Belgium	68 (6.9)	0 (0.0)	68 (3.4)
Canada	82 (8.3)	95 (9.4)	177 (8.9)
Germany	102 (10.4)	0 (0.0)	102 (5.1)
Spain	37 (3.8)	29 (2.9)	66 (3.3)
France	60 (6.1)	75 (7.4)	135 (6.8)
Greece	48 (4.9)	43 (4.3)	91 (4.6)
Italy	0 (0.0)	63 (6.3)	63 (3.2)
Ireland	0 (0.0)	19 (1.9)	19 (1.0)
Norway	45 (4.6)	0 (0.0)	45 (2.3)
Netherlands	67 (6.8)	64 (6.4)	131 (6.6)
New Zealand	0 (0.0)	25 (2.5)	25 (1.3)
Russia	129 (13.1)	76 (7.5)	205 (10.3)
Sweden	29 (3.0)	0 (0.0)	29 (1.5)
Finland	0 (0.0)	49 (4.9)	49 (2.5)
Turkey	43 (4.4)	0 (0.0)	43 (2.2)
United Kingdom	69 (7.0)	124 (12.3)	193 (9.7)
United States	159 (16.2)	157 (15.6)	316 (15.9)
South Africa	0 (0.0)	94 (9.3)	94 (4.7)

Provide the following information for utilization in the review process of your application by close of business on May 21, 2008, with the exception of Clinical comment #1. Provide a response to comment #1 within the next one-two weeks.

As there were 2 clinical information requests, it is not clear if the May 21 date or the 1-2 week turnaround applies to the second clinical query. Please clarify?

Please let me know if you have any questions or comments. I may be receiving some addition internal feedback on the points identified above by the close of business on Monday so these should be considered drafts, I wanted to give you a little advanced notice.

As you might have anticipated, the approval of the Advair exacerbations labeling on 30 April has churned up a lot of questions in our shop...we are likely to be sending the Division a request to clarify specific issues that relate to our ongoing NDA and sNDA reviews for the HandiHaler and Respimat as well as ongoing/planned clinical trials in other development programs.

Best regards,

Jeffrey R. Snyder
Executive Director
Drug Regulatory Affairs
a Boehringer Ingelheim Pharmaceuticals, Inc.
Ph. 203.778.7727
FAX 203.837.4928
cell (b) (6)
jeff.snyder@boehringer-ingelheim.com

NDA 21-936

Clinical Response to Sponsor questions (e-mail from Jeff Snyder)

Question 1:

There are 4 primary endpoints for studies 205.254/255: are all 4 the subject of this request?

Division response:

Subgroup analysis for trough FEV₁ and exacerbation primary endpoints are requested.

Question 2:

Should the subgroup analyses be based on the pooled studies (otherwise the subgroups get really small)?

Division response:

Complete the subgroup analysis on the pooled analysis.

Question 3:

The combined report for 205.254/255 (U05-2249) contains hypothesis tests (trough FEV₁, SGRQ and TDI) for heterogeneity of treatment effect among the countries (20 countries). None of these tests suggested heterogeneity.

The primary endpoints are not powered for sub-group analyses by country. Would a sub-group analysis by region where countries are split into two regions address your concerns? The table below shows the number of patients treated in each study in each country. Can you tell us which country you would like in each region?

Division response:

We acknowledge that the endpoints are not powered for sub-group analyses by country. Subgroup analysis by region is acceptable as long as the United States is analyzed separately. You may group countries into regions as geographically appropriate.

Question 4:

As there were 2 clinical information requests, it is not clear if the May 21 date or the 1-2 week turnaround applies to the second clinical query.

Division response:

The May 21 date applies to the second clinical query (subgroup analysis by country/region).

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/s/

Miranda Raggio
5/8/2008 11:15:13 AM
CSO



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

FACSIMILE CORRESPONDENCE

Date: April 24, 2008

To: Jeffrey R. Snyder

Company: Boehringer Ingelheim

Phone: 203-778-7727

Fax: 203-837-4928

From: Miranda Raggio, RN, BSN, MA
Regulatory Health Project Manager
Division of Pulmonary and Allergy Products

Phone: 301-796-2109

Subject: NDA 21-936 CMC Information Request

of Pages: 5

Comments: Please call with any questions. Thanks, miranda

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received this document in error, please notify us immediately by telephone at
(301) 796-2109. Thank you.**

We are currently reviewing your NDA dated November 16, 2007, received November 16, 2007, for SPIRIVA Respimat. Provide the following information for utilization in the review process of your application by close of business on May 21, 2008, with the exception of Clinical comment #1. Provide a response to comment #1 within the next one-two weeks.

Clinical

1. Provide a separate analysis of COPD exacerbations for protocols 205.254 and 205.255.
2. Provide a subgroup analysis of the primary endpoint for protocols 205.254 and 205.255. Sort data by country/region.

CMC

3. Provide data to justify the (b) (4) maximum holding period for the bulk solution formulation in the stainless steel production tank, as indicated in your Master Batch Records for the (b) (4) batch, and indicate if this is the same for the commercial batch scale.
4. Provide an agreement to revisit the extractable specifications for the Respimat components when sufficient data are obtained, so that the specifications are more appropriate for controlling the quality of critical materials of the Respimat device. Propose an approximate length of time needed for fulfillment of this agreement.
5. Regarding the Respimat A5, clarify anticipated batch sizes so that the sampling table (013841-06) may be better understood. Justify the acceptance of a small percentage of inhalers requiring more than 75 cocking procedures for locking. Justify the acceptance criterion allowing innumerable inhalers with as many as 75 cocking procedures for locking. Clarify the reason for the lack of performance parameters in the specifications. Clarify the typically observed foreign body or material residue contamination.
6. Regarding the aluminum cylinder with air hole seal, clarify anticipated batch sizes so that the sampling table (019957-03) may be better understood. Clarify why the defects listed as “defect class 2A” are acceptable for a given percentage of the aluminum cylinders and how they will yield an acceptable drug product.
7. Provide an agreement to revisit the extractable specifications for the cartridge container components, and the plastic cap with sealing ring, when sufficient data are obtained, so that the specifications are more appropriate for controlling the quality of the critical materials of the container closure system. Propose an approximate length of time needed for fulfillment of this agreement.
8. Clarify anticipated batch sizes so that the sampling table (019957-03) for the plastic cartridge container may be better understood. Clarify the typically observed foreign body or material residue contamination and indicate its’ location

on the container. Clarify why the defect “container not fully formed or precisely cut [REDACTED] (b) (4) is not a critical defect.

9. Clarify anticipated batch sizes so that the sampling table (019957-03) for the plastic cap with sealing ring may be better understood.
10. Clarify the nature of the typically observed processing and assembly defects for the plastic cap and sealing ring, and clarify why allowing a small percentage of defects in accordance with the sampling table does not compromise the quality of the drug product. Provide a similar response pertaining to allowing a small percentage of closures which fail the dimensional acceptance criteria.
11. Clarify the reason for conditioning the cartridges [REDACTED] (b) (4)
[REDACTED]
12. Provide the fill target and allowed range for filling the cartridges during manufacture.
13. Rectify the following discrepancy: Your characterization study (volume 1.2, pages 78-80) recommends repriming with one actuation if the product is not used for more than three days. The draft Patient Instructions for Use has changed this to repriming with one actuation if the product has not been used for more than [REDACTED] (b) (4).
14. Clarify how the “outer bag” of the cartridge is in direct contact with the formulation (volume 1.2, page 130).
15. Revise your drug product specification sheets to include the number of drug product units tested for each specification, as well as the number of actuations employed per canister (e.g., for the aerodynamic particle size distribution tests).
16. Clarify the reasons for using [REDACTED] (b) (4) overfill in the drug product.
17. Provide information about the ruggedness of the Respimat locking mechanism and the possibility of the patient defeating this mechanism.
18. Provide a reference to the location of information provided in the IND and NDA for the Spiriva Respimat drug product for manufacturing and control of the 0.045% comparator product (5 µg per spray) used in clinical studies. Include, for example, representative release and stability data and representative performance data.
19. Clarify any controls on the amount of force required to insert and properly seat the cartridge in the device. Comment on the difficulty of this process for patients, especially elderly patients.

20. Provide representative individual dose data across the life of the drug product using the laser diffraction method for aerodynamic particle size distribution.
21. Pertaining to extractable specifications for various components which do not set lower limits (e.g. for oligomers) clarify the basis for a lack of lower limits in these acceptance criteria, especially with regards to the possibility that certain levels of extractables are characteristic of the materials used in the components.
22. Additional CMC comments, including comments pertaining to the supporting Drug Master Files for this, application may be provided in the future.
23. Submit revised draft labeling incorporating the following preliminary labeling comments:
 - a. The following comments pertain to the carton labels:
 - (1) Correct the misspelling of “excursions”.
 - (2) Improve the prominence of the established name on the carton labels.
 - b. The following comment pertains to the cartridge and device label:
 - (1) Improve the legibility of the cartridge label, and of the device label which contains the counter scale.

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

NDA 21-936

Drafted by: Miranda Raggio/April 21, 2008
Initialed by: Sandy Barnes/April 22, 2008
Alan Schroeder/April 23, 2008
Ali Al-Hakim/April 24, 2008
Theresa Michele/April 24, 2008
Sally Seymour/April 24, 2008
Finalized by: Miranda Raggio/April 24, 2008

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/s/

Miranda Raggio
4/24/2008 09:17:43 AM
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Miranda Raggio
4/24/2008 09:18:06 AM
CSO



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

FACSIMILE CORRESPONDENCE

Date: March 26, 2008

To: Jeffrey R. Snyder

Company: Boehringer Ingelheim

Fax: 203-778-7727

Phone: 203-837-4928

From: Miranda Raggio, RN, BSN, MA
Regulatory Health Project Manager
Division of Pulmonary and Allergy Products

Phone: 301-796-2109

Subject: NDA 21-936 CMC Information Request

of Pages: 5

Comments: Please call with any questions. Thanks, miranda

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received this document in error, please notify us immediately by telephone at
(301) 796-2109. Thank you.**

We are currently reviewing your NDA dated November 16, 2007, received November 16, 2007, for SPIRIVA Respimat. We request that you provide the following information for utilization in the review process of your application by close of business on April 21, 2008.

1. Provide information and test results pertaining to any residual (b) (4) in the drug product formulation in the cartridges as a result of the sterilization of the container closure components.
2. You have indicated that the Respimat product locks after dispensing 30 (b) (4) doses. Since it may take 5 actuations or more to prime the product, this represents a loss of (b) (4) doses out of the labeled 30 doses in the unit in situations when the device locks after 30 doses. Address this issue to allow for a reasonable number of priming actuations without loss of doses available to the patient.
3. Provide the summaries of the methods used and available validation data for the drug product leachables testing since the leachables data have been used to demonstrate that it is not necessary to perform routine drug product leachables testing.
4. Provide data pertaining to the levels, if any, of (b) (4) observed in the drug product during stability studies.
5. Clarify whether any validation studies were performed for the control extraction and leachable methods.
6. Indicate the volumes of placebo solution used and the number of components in each volume for the simulated leachables testing for the critical Respimat components.
7. Clarify why you have provided non-clinical reports of the results of USP <87> and USP <88> testing for the Handihaler instead of for the case upper part of the Respimat device (Vol. 3).
8. Clarify how the activity of the benzalkonium chloride excipient from different manufacturers is controlled, or alternatively, specify the manufacturer used in development and use the same source for the commercial product.
9. Provide any available data comparing the two HPLC-MS methods for impurities described in method #020538 for impurities, using the same samples. Clarify which data in the NDA were obtained with each method.
10. Clarify the reason that in the batch release data there is a tendency for mean spray content to be somewhat low, relative to the labeled claim, whereas the mean pump delivery tends to be quite close to the target. Clarify the reason for the

tendency for increase in delivered dose (mean spray content) over the life of the unit.

11. Provide an agreement to reevaluate the drug product specifications (acceptance criteria) as more release and stability data pertaining to commercial batches is obtained, so that the acceptance criteria are representative of the expanded data as well as of the clinical batches.
12. The following comments pertain to the specification for aerodynamic particle size distribution (APSD) using the cascade impactor (method 020208).
 - a. This comment pertains to your analytical procedure. Provide justification of the system suitability test criterion for mass balance, or modify it to reflect representative data, considering that each APSD test result is based on 4 doses (8 actuations), rather than being based on individual actuations.
 - b. Develop and institute a specification for individual units as well as for the mean of three units. This applies to both methods 020208 and 020209.
 - c. Modify the proposed Andersen Cascade Impactor stage and component groupings for APSD by splitting Group 1 into two new groups (i.e., Mouthpiece-adapter, SIP and Stage 0 in one group, and Stages 1 and 2 in another group), and set the acceptance criteria for these new stage groupings based upon your data, for improved control of the APSD.
 - d. Data which you used to develop APSD-cascade impactor specifications include two of the drug product batches used in the pivotal clinical studies (i.e., batches #202820-WE01070189 and #202948-WE01070187). The release and stability data from these two batches are consistently at or above the midpoint of the acceptance criterion range for the critical stage group 2 (i.e., (b) (4) of label claim). The proposed acceptance criterion for stage group 2, however, allows a minimum of (b) (4) of label claim. Provide justification with additional data for the proposed acceptance criterion for Group 2, or modify it to better reflect the data from the clinical batches.
13. The following comments pertain to specifications for APSD using the alternative laser diffraction method (method 020209).
 - a. Develop and institute acceptance criteria for individual units as well as for the mean of three units.
 - b. Modify the particle size ranges of the groupings for APSD by splitting Group 1 into two new groups (i.e., SIP and Stage 0 in one group, and Stages 1 and 2 in another group), and set the acceptance criteria for these new stage groupings based upon your data.

- c. Provide clarification to show that the APSD data obtained are of a representative sampling of the entire plume.
- d. Specify in the “apparatus” section of the method that it is the (b) (4) instrument that is used for this method (as indicated in the section on instrument settings).
- e. Provide more details of the measurement of the APSD, such as the following information.
 - 1. Provide additional information identifying and describing the additional components used in the test (besides the (b) (4) instrument).
 - 2. Clarify the time that the measurement takes place relative to the time of actuation of the drug product, the duration of measurement relative to the time of actuation, and the part of the plume that is tested.
 - 3. Provide more details of the overall apparatus set up including the laser diffraction instrument and the additional components, including fixed dimensions among the instrument, its additional components, the laser beam and the Respimat inhaler. Explain how sampling is accomplished with the use of an airflow.
 - 4. Specify, as appropriate, the software and version used in this instrument. Provide representative single actuation data.

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

NDA 21-936

Drafted by Miranda Raggio/3-24-08

Initialed by Sandy Barnes/3-25-08

Alan Schroeder/3-26-08

Ali Al-Hakim/3-26-08

Finalized by Miranda Raggio/3-26-08

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/s/

Miranda Raggio
3/26/2008 01:44:37 PM
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Miranda Raggio
3/26/2008 01:44:58 PM
CSO



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

FACSIMILE CORRESPONDENCE

Date: March 13, 2008

To: Jeffrey R. Snyder

Company: Boehringer Ingelheim

Phone: 203-778-7727

Fax: 203-837-4928

From: Miranda Raggio, RN, BSN, MA
Regulatory Health Project Manager
Division of Pulmonary and Allergy Products

Phone: 301-796-2109

Subject: NDA 21-936 Labeling Comments

of Pages: 4

Comments: Please call with any questions. Thanks, miranda

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other action based on the content of this communication is not authorized. If you have
received this document in error, please notify us immediately by telephone at
(301) 796-2109. Thank you.**

We are currently reviewing your NDA dated November 16, 2007, received November 16, 2008, for SPIRIVA Respimat. We have the following comments regarding your proposed labeling and the Physician Labeling Rule deficiencies.

Highlights

1. The new rule [21 CFR 201.57(a)(6)] requires that if a product is a member of an established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights:

“(Drug/Biologic Product) is a (name of class) indicated for (indication(s)).”

Please revise the Indications and Usage section of Highlights to read
“*SPIRIVA Respimat is an anticholinergic indicated for...*”

3. Refer to 21CFR 201.57 (a) (11) regarding what information to include under the Adverse Reactions heading in Highlights. Remember to list criteria used to determine inclusion (e.g. incidence rate).

Full Prescribing Information (FPI)

1. The proprietary and established names can be repeated at the beginning of the FPI, or at the beginning of each page of the FPI (e.g. as a header), if this enhances product identification on subsequent pages of labeling.
2. Adverse reactions within a category of the Adverse Reactions section of the FPI, or in a table or listing, must be listed in decreasing order of frequency.
3. In the Clinical Studies Section of the FPI include a summary statement about the effects in age, gender, and racial subgroups.
4. Do not refer to adverse reactions as “adverse events.” Please refer to the “Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format,” available at <http://www.fda.gov/cder/guidance>.
5. In How Supplied/Storage and Handling, include information as required under 21 CFR 201.57© (17), e.g. dosage strength. Include information on available dosage forms to which the labeling applies and for which the manufacturer or distributor is responsible, including strength and potency of dosage form in metric system (e.g., 10milligram tablets)
6. Patient Counseling Information must follow after How Supplied/Storage and Handling section. [See 21 CFR 201.56(d) (1)] This section must not be written for the patient but rather for the prescriber so that important information is conveyed to the patient to use the drug safely and effectively. [See 21 CFR 201.57 (c) (18)]

7. The Patient Counseling Information section must reference any FDA-approved patient labeling or Medication Guide. [See 21 CFR 201.57(c)(18)] The reference [See FDA- Approved Patient Labeling] or [See Medication Guide] should appear at the beginning of the Patient Counseling Information section to give it more prominence.
8. There is no requirement that the Patient Package Insert (PPI) or Medication Guide (MG) be a subsection under the Patient Counseling Information section. If the PPI or MG is reprinted at the end of the labeling, include it as a subsection. However, if the PPI or MG is attached (but intended to be detached) or is a separate document, it does not have to be a subsection, as long as the PPI or MG is referenced in the Patient Counseling Information section.
9. Any FDA-approved patient labeling must be appended to or accompany the labeling as a separate document (Note: This requirement is in effect as of June 30, 2007).

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

NDA 21-936

Drafted by Miranda Raggio/3-11-0-8

Initialed by Sandy Barnes/3/13/08

Theresa Michele/3/13/08

Sally Seymour/3/13/08

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/s/

Miranda Raggio
3/13/2008 02:33:00 PM
CSO

Miranda Raggio
3/13/2008 02:33:20 PM
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FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Meeting Type: Telecon

Meeting Category: Information Request

Meeting Date and Time: February 26, 2008

Meeting Location: White Oak Building, Room 3201

Application Number: NDAs 21-936 and 21-395, IND 46,687

Product Name: Spiriva Respimat/Spiriva HandiHaler

Received Briefing Package N/A

Sponsor Name: Boehringer Ingelheim

Meeting Requestor: FDA

Meeting Chair: Sally Seymour, M.D., Acting Deputy Director

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

Meeting Attendees:

FDA Attendees:

Sally Seymour, M.D., Acting Deputy Director & Medical Team Leader, Division of Pulmonary and Allergy Products

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

Charles Lee, M.D., Medical Team Leader, Division of Pulmonary and Allergy Products

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

Peter Starke, M.D., Associate Director of Safety

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

Ladan Jafari, Regulatory Project Manager, Division of Pulmonary and Allergy Products

Sponsor Attendees:

Dr. Chris Corsico, Vice President, Drug Safety and Information (DSI), Drug Regulatory Affairs, Boehringer Ingelheim

Dr. Mike Tsianco, Vice President, Biometrics and Data Management (BDM), Boehringer Ingelheim

Dr. Shailendra Menjoge, District Biostatistics, Boehringer Ingelheim

Dr. Harry Ulrich, Associate Director, DSI, Boehringer Ingelheim

Dr. Steven Lanes, District Clinical Scientist, DSI, Boehringer Ingelheim

Dr. Michele Jara, Sr. Associate Director, DSI, Boehringer Ingelheim

Dr. Steven Kesten, Group Leader, Respiratory, Corporate Department, Medical Affairs, Boehringer Ingelheim

Dr. Uli Vogel, Corporate, Drug Safety, Boehringer Ingelheim

Ms. Tacy Pack, Director, Drug Regulatory Affairs, Boehringer Ingelheim

Jeffrey Snyder, Executive Director, Drug Regulatory Affairs

Background

In the November 30, 2007, Information Amendment to IND 46,687 Boehringer Ingelheim (BI) noted a potential association between tiotropium and stroke adverse events. On February 21, 2008, the Division requested a teleconference with BI to discuss this signal, along with their intent to issue a Public Health Advisory for inadvertent swallowing of Spiriva HandiHaler capsules and an issue related to the Advisory Committee (AC) for NDA 21-936. The teleconference was arranged for February 26, 2008, at 4:15pm. The discussion highlights are below.

Discussion

The Division opened the discussion by stating that there were three issues to be discussed. The first issue involved the planned AC meeting for Spiriva Respimat, which had been recently cancelled. The Division asked BI if they were aware of the AC meeting cancellation. BI responded that they had been notified of the cancellation.

The Division next informed BI that a Public Health Advisory (PHA) would be released related to the inadvertent swallowing of Spiriva HandiHaler inhalation capsules, noting that this release would be similar to the information published in the Drug Topics article in 2005 (Drug Topics, April 4, 2005, page 48; www.drugtopics.com). The Division acknowledged that BI had a labeling supplement currently under review to address this issue. BI acknowledged the PHA and no further discussion occurred.

The Division then focused on the main purpose of the teleconference, the potential stroke safety signal with tiotropium. The Division acknowledged the November 30, 2007, submission and inquired if there was a reason BI looked at the safety data initially. BI responded that the stroke

Application Number # NDAs 21395 and 21936, IND 46687

adverse events were found while performing routine analysis for pharmacovigilance. The data resulting from this routine analysis was what generated the November 30, 2007, submission to the FDA.

The general proposed plan to address the stroke signal and related safety concerns was then presented to BI by the Division. The Division highlighted the following elements of this plan:

1. Establishment of a timeline of relatively short duration for this safety review.
2. The intent to look further into the data to evaluate the signal and its strength.
3. To communicate this safety information to the public as early as possible.

The communication is consistent with the FDA's commitment for early communication of potential health risks. The Division acknowledged that there would be opportunity to revise the communication, if necessary, as new data are received and reviewed in the future.

The Division stated that they would need the support of BI with respect to safety data, and gave an overview of the additional information that would need to be submitted. The Division indicated that an information request would be forthcoming, requesting the following information:

1. Demographic information for all patients enrolled in the 29 controlled studies
2. Past medical history, including potential stroke risk factors for those patients who had a stroke related adverse event
3. Concomitant medications
4. Case report forms related to stroke and death
5. Data related to stroke adverse events

In response to questions posed by the Division, BI stated that they would be able to extract past medical history data as reported by Principal Investigators, demographic risk factors such as smoking, race, etc., and concomitant medications. They noted that concomitant medications would need to be specifically selected (i.e., aspirin, ibuprofen, etc) and that they did not collect family medical history information on study participants.

The Division asked BI how long they thought it may take them to pull this information together. BI responded that they could most likely get the majority of the data to the Division in a relatively short period of time.

BI noted that the Data Monitoring Safety Board (DSMB) for UPLIFT was aware of the stroke data and recommended the trial proceed. BI inquired if the Division wanted to speak to the DSMB. The Division indicated that they do not typically speak directly with the DSMB. BI asked if the data reviewed by the DSMB for the UPLIFT trial would be helpful to the Division. The Division stated that if BI thought this information would be useful, then BI was welcome to submit the information.*

The Division alerted BI that the timeline for the early communication was approximately 30 days, and that as data was reviewed the timeline may be adjusted accordingly. Both parties acknowledged that further discussion related to this issue would most likely be needed.

Application Number # NDAs 21395 and 21936, IND 46687

The Division indicated that the information request would be conveyed to BI in the next few days. The meeting was adjourned with BI stating that they would contact the Division with questions regarding the information request when it was received.

*Post meeting note: The Division does not want to encourage submission of data that may jeopardize the blinding of the ongoing UPLIFT trial.

Drafted by: Miranda Raggio/February 27, 2008

Initialed by: Peter Starke/February 28, 2008

Sally Seymour/February 28, 2008

Finalized by: Miranda Raggio 29, 2008

APPEARS THIS WAY ON ORIGINAL



Linked Applications

Sponsor Name

Drug Name

IND 46687

BOEHRINGER
INGELHEIM
PHARMACEUTICALS
INC

BA 679 BR(TIOTROPIUM
BROMIDE)POWDER INH

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/s/

MIRANDA B RAGGIO

02/29/2008

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Miranda Raggio
2/29/2008 10:58:00 AM
CSO



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

FACSIMILE CORRESPONDENCE

Date: February 4, 2008

To: Jeffrey R. Snyder

Company: Boehringer Ingelheim

Fax: 203-778-7727

Phone: 203-837-4928

From: Miranda Raggio, RN, BSN, MA
Regulatory Health Project Manager
Division of Pulmonary and Allergy Products

Phone: 301-796-2109

Subject: NDA 21-936 CMC Information Request

of Pages: 3

Comments: Please call with any questions. Thanks, miranda

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received this document in error, please notify us immediately by telephone at
(301) 796-2109. Thank you.**

NDA 21-936

We are currently reviewing your NDA dated November 16, 2007, received November 16, 2007, for SPIRIVA Respimat. We request that you provide the following information for utilization in the review process of your application by close of business on February 11, 2008.

1. Provide a rationale for combining the Adaptor-mouthpiece, Standard Induction Port (SIP) and Stages 1-2 of the Andersen Cascade Impactor in Group 1 during measurement of the APDS for the drug product. We note that there is a substantial amount of drug deposited in Group 1 as a result of this combination.
2. Provide three samples of the SPRIVIA Respimat drug product.

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

NDA 21-936

Drafted by: Miranda Raggio/2-4-08

Initialed by: Ladan Jafari for Sandy Barnes/2-4-08

Prasad Peri/2-4-08

Ali Al-Hakim/2-4-08

Finalized by: Miranda Raggio/2-4-08

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this page is the manifestation of the electronic signature.**

/s/

Miranda Raggio
2/4/2008 02:41:54 PM
CSO

Miranda Raggio
2/4/2008 02:42:13 PM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-936

Boehringer Ingelheim
900 Ridgebury Road
PO Box 368
Ridgefield, CT 06877-0368

Attention: Jeffrey R. Snyder
Executive Director
Drug Regulatory Affairs

Dear Mr. Snyder:

Please refer to your new drug application (NDA) dated November 16, 2007, received November 16, 2007 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Spiriva® Respimat®(tiotropium bromide inhalation spray).

We also refer to your submissions dated January 4, 2008, and January 10, 2008.

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**. Therefore, the user fee goal date is September 16, 2008.

During our filing review of your application, we have not identified any potential review issues.

However, we request that you submit the following information:

1. Provide any foreign post-marketing safety data for the SPIRIVA Respimat available at the time of the four month safety update. Include a summary and analysis of these data.
2. Provide a literature review for tiotropium from the time of the SPIRIVA Handihaler NDA submission (December 2001) to the present.
3. Provide a summary and analysis of post-marketing adverse events for any SPIRIVA HandiHaler from July 2005-present.

4. Provide a summary of SPIRIVA Handihaler safety data from controlled clinical trials with a cut off date of July 2007 or later. Specific emphasis should be placed on mortality and cardiovascular adverse events. In addition, provide a complete clinical study report for any trials focused on cardiac outcomes.
5. Provide any available data from the UPLIFT trial. Include a summary and analysis of these data.

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

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies for this application for all pediatric patients.

If you have any questions, call Miranda Raggio, Regulatory Project Manager, at (301) 796-796-2109.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Division Director
Division of Pulmonary and Allergy Products
Center for Drug Development and Research

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/s/

Badrul Chowdhury
1/29/2008 11:20:45 AM

NDA 21936



FOOD AND DRUG ADMINISTRATION

Meeting Type: Regulatory Briefing

Meeting Category: Safety

Meeting Date and Time: July 18, 2008, 1-3pm

Meeting Location: Food and Drug Administration
10903 New Hampshire Ave.
Shared Services Building, Conference Room 2047
Silver Spring, MD 20993

Application Number: NDA 21,936

Product Name: Spiriva Respimat®

Sponsor Name: Boehringer Ingelheim

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

Meeting Chair: John K. Jenkins, M.D., Director
Office of New Drugs

Meeting Recorder: Miranda Raggio, M.A., RN, Regulatory Project
Manager, Division of Pulmonary and Allergy
Products

1.0 BACKGROUND

Boehringer Ingelheim (BI) submitted NDA 21-936 for Spiriva Respimat® (tiotropium bromide inhalation spray) on November 16, 2007. This NDA is currently under review in the Division of Pulmonary and Allergy Products (DPAP). Spiriva HandiHaler®, which also contains tiotropium bromide in a single dose dry powder formulation, is an approved and marketed product.

Spiriva Respimat

In November 2005, upon the unblinding of two 1-year Phase III clinical trials for Spiriva Respimat®, a mortality imbalance in favor of placebo was noted. The Division of Pulmonary and Allergy Products (DPAP) presented this issue to the Drug Safety Oversight Board (DSOB) in June 2006. The DSOB determined that there was a “weak” safety signal, mostly likely attributable to the unusually low mortality rate in the placebo group. The DSOB recommended additional follow-up of patients who had discontinued the study for the purpose of determining post-study vital status. No action with regards to the approved product, Spiriva HandiHaler®, was recommended at that time. Upon review of follow-up vital status data submitted as part of the Spiriva Respimat® NDA, the Division determined that differential drop-out could explain a portion of the mortality signal, but further data would be needed to explain the remaining signal and to confirm the safety.

Spiriva HandiHaler

Spiriva HandiHaler® (tiotropium bromide inhalation powder) was approved for the long-term, once daily, maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema on January 30, 2004.

In a submission to the Spiriva HandiHaler® IND 46,687 on November 30, 2007, BI provided a preliminary analysis of pooled data from routine safety monitoring of 29 clinical trials, which revealed a potential increased risk of stroke adverse events with tiotropium. DPAP responded to this notice of a potential stroke safety signal by placing an OSE consult, requesting additional patient level data from the sponsor to perform an independent analysis, and asking the Department of Veterans Affairs to provide an epidemiologic analysis of their databases for incidents associated with ipratropium/tiotropium and stroke. Additionally, an early communication regarding this potential stroke signal was issued in March 2008.

The potential mortality and stroke signals, from the Respimat® and HandiHaler® products, respectively, prompted DPAP to request a regulatory briefing to discuss these safety signals associated with tiotropium bromide (active drug in both products), and to determine their impact on the Spiriva Respimat® NDA currently under review.

The UPLIFT Trial

Two days prior to the regulatory briefing, BI submitted preliminary data from the Understanding the Potential for Long-Term Impact on Function with Tiotropium (UPLIFT) trial, a 6000 patient, randomized, double-blind, placebo-controlled trial evaluating the effect of Spiriva® on COPD disease progression over a 4-year follow-up period. Preliminary safety data did not demonstrate an increased risk of stroke or all-cause mortality in the tiotropium group compared to placebo.

2.0 DISCUSSION

Following Dr. Jenkins' introduction, Dr. Sally Seymour provided an introductory slide presentation which stated the objectives of the meeting, summarized the Spiriva Respimat® NDA/mortality issues and the Spiriva®/stroke issues, and presented the questions to the panel for discussion. Dr. Theresa Michele then gave an in depth slide presentation of the Spiriva Respimat® NDA delineating the specific data which prompted the mortality safety concerns. Dr. Banu Karimi-Shah concluded the presentation by offering a detailed summary of the Spiriva HandiHaler®, focusing on the potential stroke signal. The floor was then open to questions and discussion.

DPAP opened the discussion by stating that prior to receipt of the preliminary UPLIFT data, a Not Approvable action for the Respimat® NDA had been anticipated, however, because the preliminary UPLIFT data were reassuring, DPAP is reconsidering the proposed action.

The discussions that followed centered on several main points:

1. The clinical trial mortality data and how "real" it is, including:
 - a. the unexpectedly low mortality rate for this COPD population in the placebo group in study 255
 - b. whether one study with a significant difference in mortality is sufficient to constitute a "real" safety signal
2. The degree to which the HandiHaler® data can be extrapolated to support the safety of the Respimat® product
3. The need for review of a complete study report from the UPLIFT trial and not rely on the preliminary findings from UPLIFT
4. Issues with the formulation

The question was raised whether the UPLIFT population was similar to the population in the Spiriva Respimat® phase III program. DPAP responded that this was not yet known, but that as BI tends to use similar inclusion criteria in their studies, it is likely that the populations are similar. UPLIFT is a multi-national trial like the 48 week phase III trials in the Spiriva Respimat® program. DPAP was encouraged to review the complete UPLIFT study report prior to using it as supportive safety data for the Respimat program.

The group went on to discuss how often one would expect to find a zero death rate over a 1-year follow up in a population with moderate to severe COPD, and noted that Study 255 showed no deaths in the placebo group during the primary study and two deaths when including the retrospective follow-up data. It was also noted that there was a dose-response relationship in the Respimat® data, demonstrating greater mortality risk in the 10 mcg than the 5 mcg dose group, but only in one study. The panel debated the statistical significance of these findings and whether one study with a significant difference in mortality is sufficient or if it is also necessary for the statistical conclusions (or at least trends) to be replicated in a second study to constitute a “real” safety signal, especially in light of the numerous safety endpoints that potentially could be examined. Various opinions were expressed by attendees throughout the discussion, including that the non-significance of the mortality data in study 254 is not adequate to rule out a mortality effect as there is variability inherent in the mortality estimates. However, it was agreed that although unresolved safety issues remain with the Respimat product, the bronchodilator efficacy of tiotropium bromide is not in question.

Both the Respimat® and HandiHaler® dispense the same drug substance, tiotropium bromide, which acts locally in the lung to produce a bronchodilatory effect. The panel discussed the extent to which a mortality effect is likely to represent a systemic rather than local pulmonary effect of the drug. There were differing opinions on the validity of using the Spiriva HandiHaler® data from the UPLIFT study to support the safety of Spiriva Respimat. Members of the audience and the panel came to no definite agreement on this issue. It was recommended that DPAP think through the approach of using safety data from Spiriva HandiHaler to support the Spiriva Respimat product.

There were comments from the panel on the multiplicity challenges and problems in the review of multiple safety endpoints in controlled clinical trials.

There was a question regarding the formulation of Spiriva Respimat®. The excipients were briefly discussed and noted to be in other inhalation products. It was generally agreed that the excipients did not raise a safety concern.

The regulatory panel generally agreed that differential drop out explains only a portion of the mortality imbalance. The panel expressed concern over the Spiriva Respimat® safety findings with regard to the mortality data and also agreed that the data do not indicate a stroke signal with the Respimat® product.

DPAP and the Panel discussed possible regulatory options. It was noted that as a very similar product (Spiriva HandiHaler®) is already on the market, there is no urgency regarding approval of Spiriva Respimat®. Therefore, DPAP should not act on the preliminary results of UPLIFT. The general consensus of the group was that the mortality data was inconclusive, and complete UPLIFT study report data should be reviewed before a determination of safety could be made.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

4.0 ACTION ITEMS

DPAP will consider discussion at today's Regulatory Briefing and take action on the Spiriva Respimat NDA.

5.0 ATTACHMENTS AND HANDOUTS

Attached are the slides presented at the meeting and the list of attendees.

Attachment 1

Meeting Attendees:

FDA Attendees

John Jenkins, M.D., FCCP, Director, Office of New Drugs
Sandy Kwedar, M.D., Deputy Director, Office of New Drugs
Curtis Rosebraugh, MD, Deputy Director, Office of Drug Evaluation II
Lee Ripper, Associate Director for Regulatory Affairs, Officer of Drug Evaluation II
Sally Seymour, M.D., Medical Team Leader, OND/ODEII/DPAP
Theresa Michele, M.D., Medical Officer, OND/ODEII/DPAP
Banu Karimi-Shah, M.D., Medical Officer, OND/ODEII/DPAP
Ruthanna Davi, Ph.D., Statistical Reviewer, OTS/OB/DBII
Miranda Raggio, RN, BSN, MA, Regulatory Project Manager, OND/ODEII/DPAP
Keith Burkhart, M.D., Medical Officer, OND
Bop Temple, M.D., Associate Director of Medical Policy, Office of Medical Policy
Stephen Grant, M.D., Medical Officer, ONDI, DCRP
John Lazor, Ph.D., Director, DCP4/OCP
Richard Pazdur, M.D., Supervisory Medical Officer, OND, OODP
Sol Sobel, M.S., Associate Director, Medical Affairs, OPS/SRS
Ana Szarfman, M.D., Ph.D., Medical Officer, Office of Translational Sciences, Office of Biostatistics, Division of Biometrics 6
Rashmikan Patel, PhD., Supervisory Chemist, OPS/OGD/DCI
Bing Cai, Ph.D., Chemist, OPS/OGD/DCI
Luqi Pei, Ph.D., Pharmacology/Toxicology Review, DPAP
Xu Wang, M.D., Medical Officer, DPAP
Neha Gada, Pharmacist, OND/ODEII/DNP
Molly Shea, Ph.D., Pharmacology/Toxicology Review, DPAP
Peter Starke, M.D., Acting Deputy Director of Safety, DPAP
David Money, R.Ph., USPHS, Office of Surveillance and Epidemiology

8/12/2008

Jack Kampf, Student Volunteer, OND/OAP
Marc Cavaille, M.D., Lead Medical Officer, OND/OAP/DSPTP
Rita Shapiro, PT, MA, DPT, Regulatory Health Education Specialist, CDER
Allen Brinker, M.D., M.S., OSE, Division of Epidemiology
Partha Roy, Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology II, Office of Clinical Pharmacology
Priscilla Callahan, M.D., Medical Officer, OND/ONP
Wiley Chambers, M.D., Supervisory Medical Officer, OND/OAP/DAIOP
Mohab Alexander, M.D., Medical Officer, OND/OODP/DMHP
Kamal Sharma, M.D., Medical Officer, OND/OODP/DBOP
Jane Gilbert, M.D., OND/ODEII/DAABP
Christina Chang, M.D., Medical Officer, OND/ONP/DNCE
Jane Liedtka, M.D., Medical Officer, OND/ODEIII/DDDP
Lanh Green, Pharm. D., M.P.H., Safety Evaluator Team Leader, DPV/OSE
Katie Laessig, M.D., Supervisory Medical Officer, OND/OAP/DAIOP
Amy Weitach, M. D., Medical Officer, OND/ODEIII/DDDP
Karin Weiss,, M.D., Deputy Director, OODP
Hari Sachs, M.D., Lead Medical Officer, OND
Julie Beitz, Acting Director (check) Office of Drug Evaluation III
Thomas Permutt, Ph.D., Supervisory Math Statistician, OTS/OB/DBII
Lisa Kammerman, Ph.D., Math Statistician, OTS/OB/DBIII
Steve Wilson, Ph.D., Division Director, OTS/OB/DBIII
Ed Nevius, Ph.D., Supervisory Math Statistician, OTS/OB
Eric Duffy, Ph.D., Supervisory Chemist, OPS/ONDQA/DPE
Wei Qiu, Ph.D, Clinical Pharmacology Team Leader, Division of Clinical Pharmacology II, Office of Clinical Pharmacology
Haw-Jyn Chiu, Staff Fellow, OND/OODP/DBOP
Sandra Casak, Staff Fellow, OND/OODP/DBOP
Qi Feng, M.D., Medical Officer, OND/OODP/DMIHP
Donald Jensen, Pharmacologist, OND/ODEI/DCRP
Ergun Velidedeoglu, Staff Fellow, OND/OAP/DSPTP

Attachment 2

Slide Presentation: Starting on next page

Minutes Drafted by Miranda Raggio/July 31, 2008

Initialed by Banu Karimi-Shah, Theresa Michele, Ruthie Davi, and Sally Seymour/August 11, 2008

Finalized by Miranda Raggio/August 12, 2008

NDA# 21-936
Tiotropium Bromide Inhalation Spray
Spiriva Respimat
Boehringer Ingelheim

Regulatory Briefing
Division of Pulmonary and Allergy
Products

July 18, 2008



Food and Drug Administration
Division of Pulmonary and Allergy Products



Objectives

- Discuss two safety signals with two different products with the same active pharmaceutical ingredient - tiotropium bromide
 - ◆ Mortality signal
 - Phase 3 program with Spiriva Respimat
 - ◆ Stroke signal
 - Pooled clinical trials with Spiriva HandiHaler

- Discuss impact of the safety signals on Spiriva Respimat NDA currently under review



Food and Drug Administration
Division of Pulmonary and Allergy Products



Regulatory Briefing

July 18, 2008

Outline

- Introduction
 - ◆ Sally Seymour, M.D.
- Spiriva Respimat NDA and Mortality
 - ◆ Theresa Michele, M.D.
- Spiriva HandiHaler and Stroke
 - ◆ Banu Karimi-Shah, M.D.
- Questions for Discussion



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Division of Pulmonary and Allergy Products



Regulatory Briefing
July 18, 2008

COPD

- Chronic Obstructive Pulmonary Disease
 - ◆ airflow limitation not fully reversible, progressive
 - ◆ symptoms - cough, sputum, dyspnea
 - ◆ risk factors - smoking, occupational exposure, genetics
 - ◆ 4th leading cause of morbidity & mortality in US
- Management
 - ◆ Pharmacotherapy
 - bronchodilators
 - anticholinergics
 - ▣ ipratropium (short acting)
 - ▣ tiotropium (long acting)
 - beta agonists
 - inhaled corticosteroids
 - oxygen



Food and Drug Administration

Division of Pulmonary and Allergy Products



Global Initiative for Chronic Obstructive Lung Disease 2005

Regulatory Briefing

July 18, 2008

Anticholinergics and COPD

- Lung Health Study – MC, R, cohort study in 6000 smokers
 - ◆ smoking intervention + ipratropium bromide
 - ◆ smoking intervention + placebo
 - ◆ usual care
- 5 year follow up suggested an increase in cardiovascular deaths in ipratropium group compared to placebo

Am J Resp Crit Care Med; 2002, 166: 333-339
- Meta-analysis of PC trials with ipratropium or tiotropium in COPD patients
 - ◆ Anticholinergics decreased the risk of respiratory death compared to placebo

J Gen Intern Med; 2006, 21:1011-1019
- ◆ Anticholinergics decreased the risk of respiratory death compared to placebo, but did not affect total mortality

Clin Rev All Immun; 2006, 219-230



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Regulatory Briefing
July 18, 2008

Tiotropium Bromide

- Long-acting anti cholinergic (anti-muscarinic)
- Bronchodilator
 - ◆ COPD
- Two unique products deliver tiotropium
 - ◆ Spiriva HandiHaler – approved in US in 2004
 - approved in > 40 countries worldwide
 - ◆ Spiriva Respimat – under NDA review in US
 - approved in five EU countries



Food and Drug Administration
Division of Pulmonary and Allergy Products

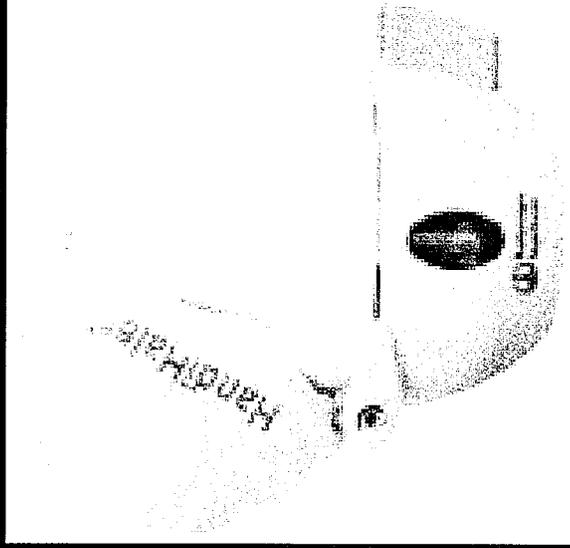


Regulatory Briefing

July 18, 2008

Spiriva HandiHaler

- Dry powder for inhalation
 - ◆ Capsules used in HandiHaler
 - ◆ 18mcg once daily
- Maintenance treatment of bronchospasm associated with COPD
- Approved 2004



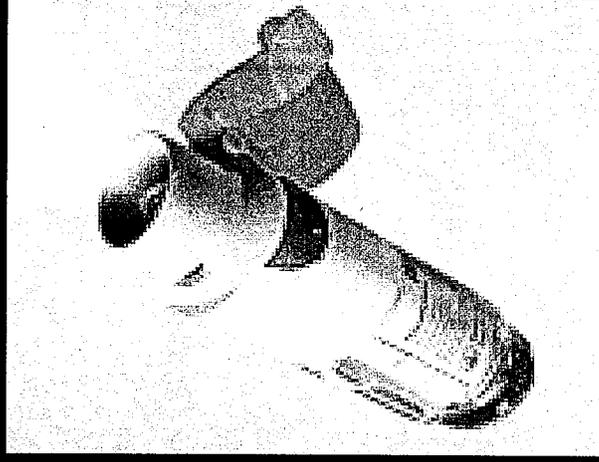
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Regulatory Briefing
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Spiriva Respimat

- NDA # 21-936 submitted November 2007
- Inhalation Spray
 - ◆ 5mcg and 10mcg once daily
- Maintenance treatment of bronchospasm associated with COPD



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Regulatory Briefing

July 18, 2008

Two Safety Signals

- Spiriva Respimat
 - ◆ Mortality imbalance in P3 clinical trials
 - Noted November 2005 after P3 trials unblinded
 - Discussed at DSOB July 2006
 - NDA submitted November 2007

- Spiriva HandiHaler
 - ◆ Stroke signal in meta-analysis of 29 controlled clinical trials with Spiriva HandiHaler and Spiriva Respimat November 2007
 - ◆ Early Communication re stroke issued March 2008



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Regulatory Briefing

July 18, 2008

UPLIFT

- Understanding the Potential for Long-Term Impact on Function with Tiotropium (UPLIFT)
 - ◆ 4 yr, R, DB, PC trial
 - ◆ assess the rate of decline of lung function
 - ◆ Spiriva HandiHaler
 - ◆ 6000 patients with COPD
- ◆ Trial completed and expect preliminary results
June – July 2008



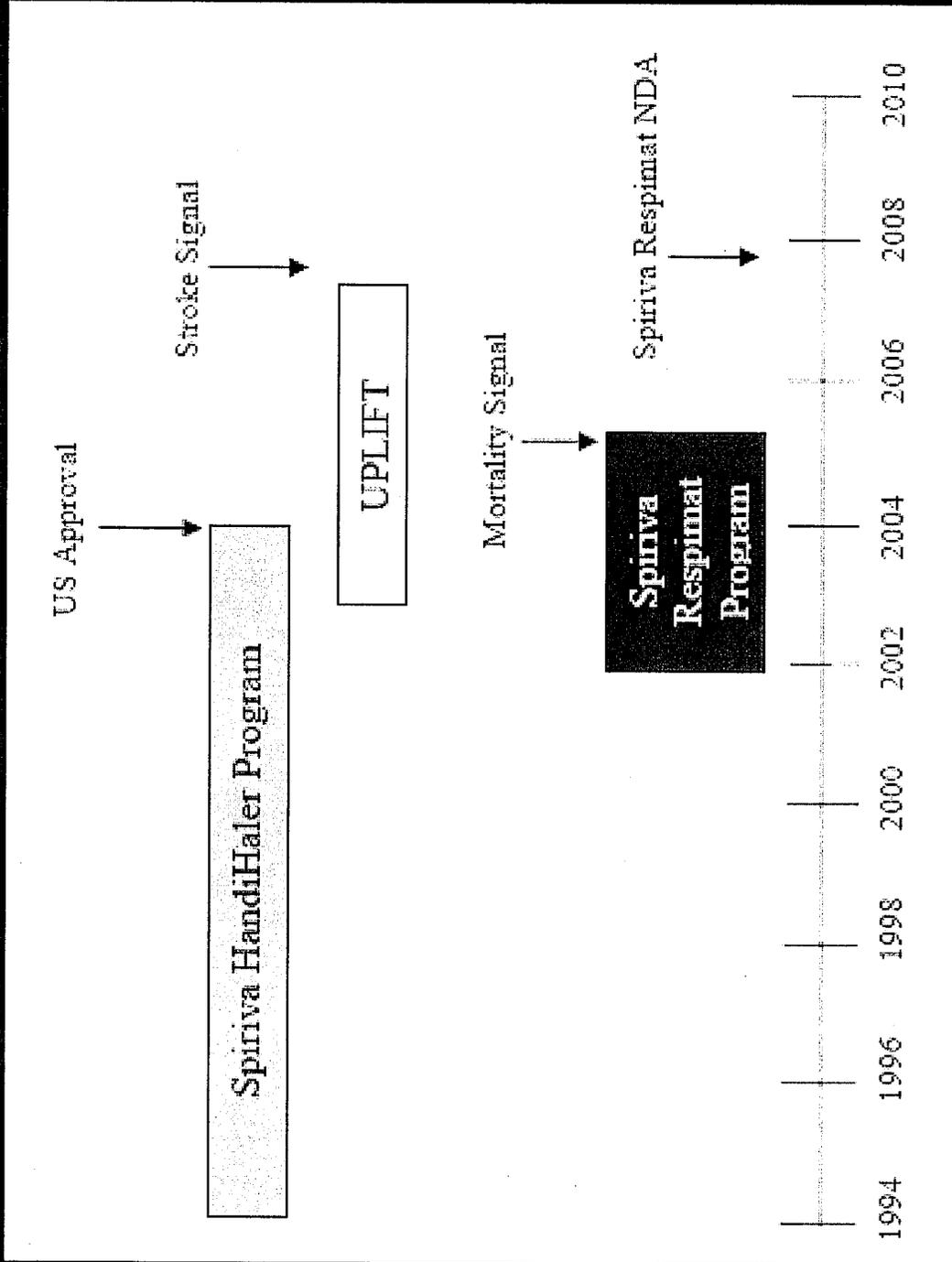
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Regulatory Briefing

July 16, 2008

Timeline



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Regulatory Briefing
July 18, 2008

Questions for Committee

- Given the uncertainty of the mortality and stroke safety signals, DPAP plans to take an NA action on the Spiriva Respimat NDA and will request submission of long term safety data from a large controlled clinical trial (UPLIFT).

Does the committee have comments regarding this approach?



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Regulatory Briefing

July 18, 2008

Questions for the Committee

- What are the committee's thoughts on the mortality data?
- What are the committee's thoughts on the stroke data?



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Regulatory Briefing
July 18, 2008

Outline

- Introduction
 - ◆ Sally Seymour, M.D.
- Spiriva Respimat NDA and Mortality
 - ◆ Theresa Michele, M.D.
- Spiriva HandiHaler and Stroke
 - ◆ Banu Karimi-Shah, M.D.
- Questions for Discussion



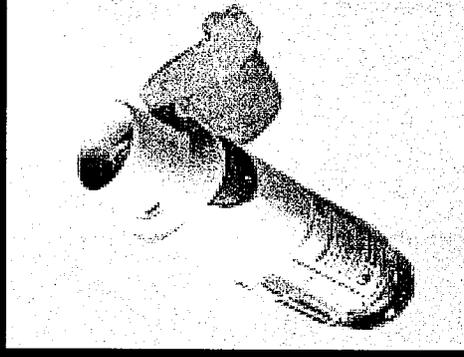
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Regulatory Briefing

July 18, 2008

Respimat Drug Development Program



- Stand-alone clinical program
- 4 pivotal studies:
 - ◆ Replicative 12-wk
 - ◆ Replicative 48-wk (1 yr)
- 4 supportive studies
 - ◆ 3-wk dose ranging
 - ◆ Single dose cross-over placebo formulation
 - ◆ Replicative 4-wk cross-over HandiHaler comparison (Phase 3)
 - ◆ HandiHaler VA study (exacerbation)



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July 18, 2008

ID	Study type	Study duration	Patient age	Treatment groups	N (ITT)	Study year	Countries
205.251	Efficacy and safety COPD	12 wks	≥40 yrs	tio R5 QD tio R 10 QD ipratr 36 mcg QID placebo	88 93 89 91	2003	Germany Italy Switzerland S Africa
205.252	Efficacy and safety COPD	12 wks	≥40 yrs	tio R5 QD tio R10 QD ipratr 36 mcg QID placebo	92 87 89 90	2003	US Canada
205.254	Efficacy and safety COPD	1 year	≥40 yrs	tio R5 QD tio R10 QD placebo	332 332 319	2005	EU N America
205.255	Efficacy and safety COPD	1 year	≥40 yrs	tio R5 QD tio R10 QD placebo	338 335 334	2005	EU N America Africa Australia
205.127	Dose ranging	3 wk	≥40 yrs	tio R1.25, R2.5, R5, R10, R20 QD tio HH 18 QD Placebo R, HH	202	1999	France



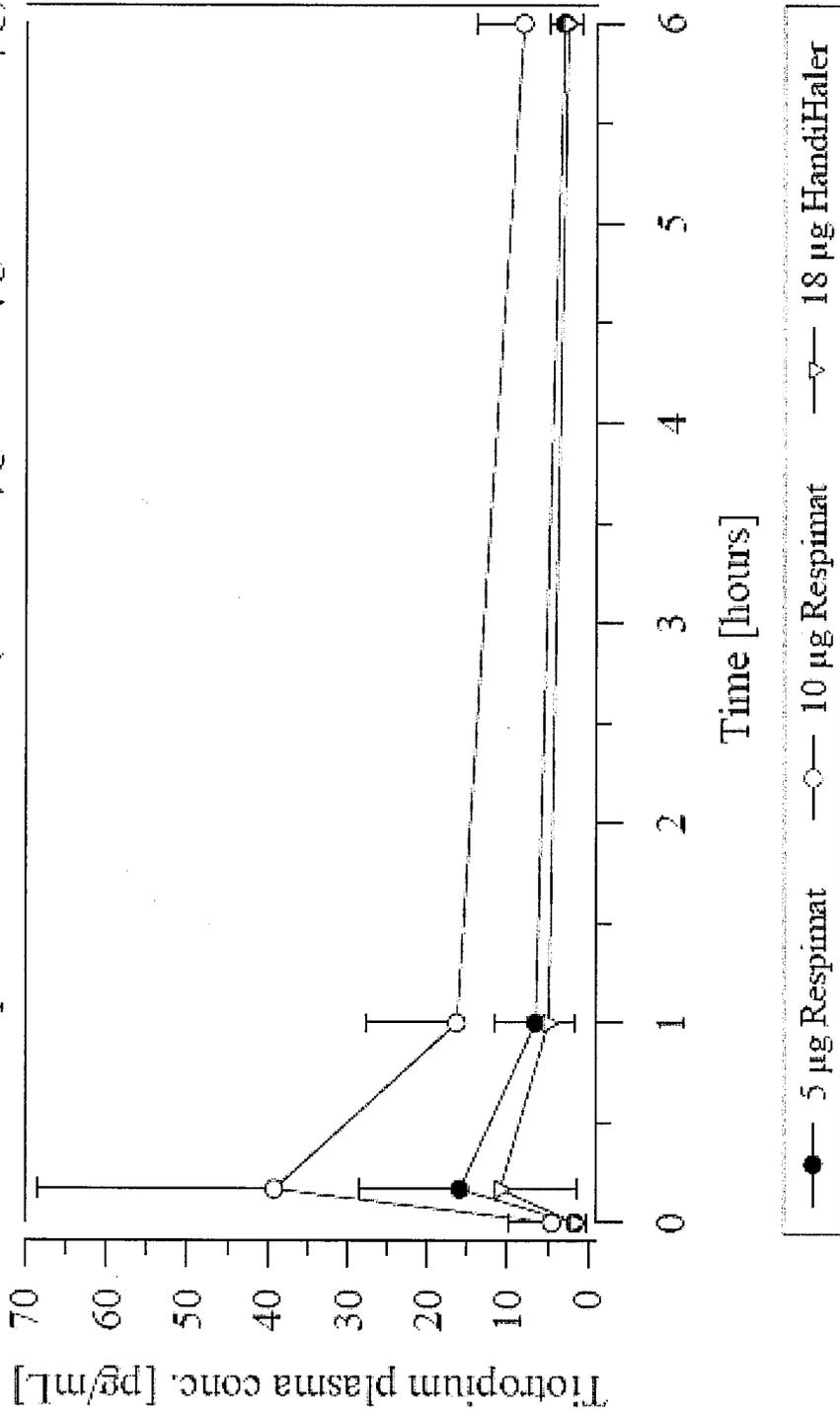
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Respimat vs. HandiHaler PK

Arithmetic mean plasma conc. \pm SD (N=53; 5 μ g and 10 μ g; N=54; 18 μ g)



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July 18, 2008

Respiamat 1 Year Pivotal Studies

- R, DB, PC, 3 parallel groups
 - ◆ Tio R5 and Tio R10
 - ◆ Multinational: 983 and 1007 subjects
 - ◆ Moderate to severe COPD (FEV₁ ≤60%)
 - ◆ Duration 336d treatment + 30d follow up = 366d
- Primary endpoints
 - ◆ 48 wk trough FEV₁
 - ◆ SGRQ
 - ◆ Mahler TDI (combined analysis)
 - ◆ Number of COPD exacerbations (combined analysis)
- Potential adverse mortality signal



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July 18, 2008

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Patient Disposition

	Tio R5 N (%)	Tio R10 N (%)	Placebo N (%)	Total N (%)
Entered	670	667	653	1990
Completed	555 (82.8)	531 (79.6)	448 (68.6)	1534 (77.1)
Discontinued				
Adverse events	115 (17.2)	136 (20.4)	205 (31.4)	456 (22.9)
Non compliant with protocol	67 (10.0)	79 (11.8)	122 (18.7)	268 (13.5)
Lost to follow-up	8 (1.2)	13 (1.9)	15 (2.3)	36 (1.8)
Consent withdrawn	9 (1.3)	11 (1.6)	15 (2.3)	35 (1.8)
Other	19 (2.8)	23 (3.4)	38 (5.8)	80 (4.0)
	12 (1.8)	10 (1.5)	15 (2.3)	37 (1.9)
Mean treatment exposure [days]	304.7	297.3	265.6	289.4



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Regulatory Briefing

July 18, 2008

Demographics

	Tio R5	Tio R10	Placebo	Total
Number of pts N (%)	670	667	653	1990
Male	491 (73.3)	498 (74.7)	487 (74.6)	1476 (74.2)
White	611 (91.2)	613 (91.9)	594 (91.0)	1818 (91.4)
Mean age [years]	64.7	65.1	65.2	65.0
Current smoker	254 (37.9)	232 (34.8)	236 (36.1)	722 (36.3)
Mean pack years	47.1	48.6	47.6	47.8
Mean FEV ₁ [L]	1.088	1.088	1.083	1.086
Mean % predicted FEV ₁	38.7%	38.5%	38.3%	38.5%



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Regulatory Briefing
July 18, 2008

Concomitant Medications

Medication	Tio R5 N=670 n (%)	Tio R10 N=667 n (%)	Placebo N=653 n (%)	Total N=1990 n (%)
Long-acting beta-agonists		not permitted		
Inhaled steroids	327 (48.8)	379 (56.8)	362 (55.4)	1068 (53.7)
Oral steroids	22 (3.3)	17 (2.5)	22 (3.4)	61 (3.1)
Xanthines	94 (14.0)	105 (15.7)	98 (15.0)	297 (14.9)
Short-acting beta-agonists		required rescue med		
Leukotriene receptor antagonists		not permitted for asthma		
Anticholinergics		not permitted†		

†40.6% of discontinued patients used short acting and 37.3% used long-acting



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Regulatory Briefing
July 18, 2008

Efficacy: 48 wk FEV1 Trough

Treatment comparison	Treatment difference			p-value*
	Mean	SE	95% C.I.	
Protocol 205.254				
Tio R5 – Placebo	0.142	0.019	(0.104, 0.181)	<.0001
Tio R10 – Placebo	0.161	0.020	(0.123, 0.200)	<.0001
Protocol 205.255				
Tio R5 – Placebo	0.113	0.017	(0.078, 0.147)	<.0001
Tio R10 – Placebo	0.140	0.017	(0.106, 0.175)	<.0001



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Division of Pulmonary and Allergy Products



Regulatory Briefing

July 18, 2008

Safety: Adverse Events

Adverse event	Tio R5 N (%)	Tio R10 N (%)	Placebo N (%)	Total N (%)
Total treated	670	667	653	1990
Any AE	505 (75.4)	525 (78.7)	502 (76.9)	1532 (77.0)
AEs leading to discontinuation	67 (10.0)	76 (11.4)	121 (18.5)	264 (13.3)
Serious AEs	108 (16.1)	125 (18.7)	110 (16.8)	343 (17.2)
Deaths	12 (1.8)	17 (2.5)	5 (0.8)	34 (1.7)
Most common AEs (>10%)				
COPD exacerbation	220 (32.8)	216 (32.4)	275 (42.1)	711 (35.7)
nasopharyngitis	94 (14.0)	64 (9.6)	54 (8.3)	212 (10.7)
dry mouth	48 (7.2)	97 (14.5)	14 (2.1)	159 (8.0)
AEs of interest				
angina	12 (1.8)	15 (2.2)	4 (0.6)	31 (1.6)
arrhythmia [†]	15 (2.2)	19 (2.8)	12 (1.8)	46 (2.3)
congestive heart failure [†]	10 (1.5)	8 (1.2)	6 (0.9)	24 (1.2)
GI hemorrhage	2 (0.3)	1 (0.1)	2 (0.3)	5 (0.3)
lung cancer [†]	9 (1.3)	8 (1.2)	7 (1.1)	24 (1.2)
myocardial infarction [†]	3 (0.4)	4 (0.6)	7 (1.1)	14 (0.7)
pneumonia	22 (3.3)	22 (3.3)	11 (1.7)	55 (2.8)
sepsis	0	0	2 (0.3)	2 (0.1)
stroke [†]	3 (0.4)	6 (0.9)	3 (0.5)	12 (0.6)

Mortality Signal Analysis

- Drug Safety Oversight Board
 - ◆ June 2, 2006
 - ◆ “Weak” safety signal; difference likely due to unusually low mortality rate in placebo group
 - ◆ Requested additional follow up on patients who discontinued to determine vital status
- Study 205.392
 - ◆ Retrospective follow up on discontinued patients from 205.254 and 205.255



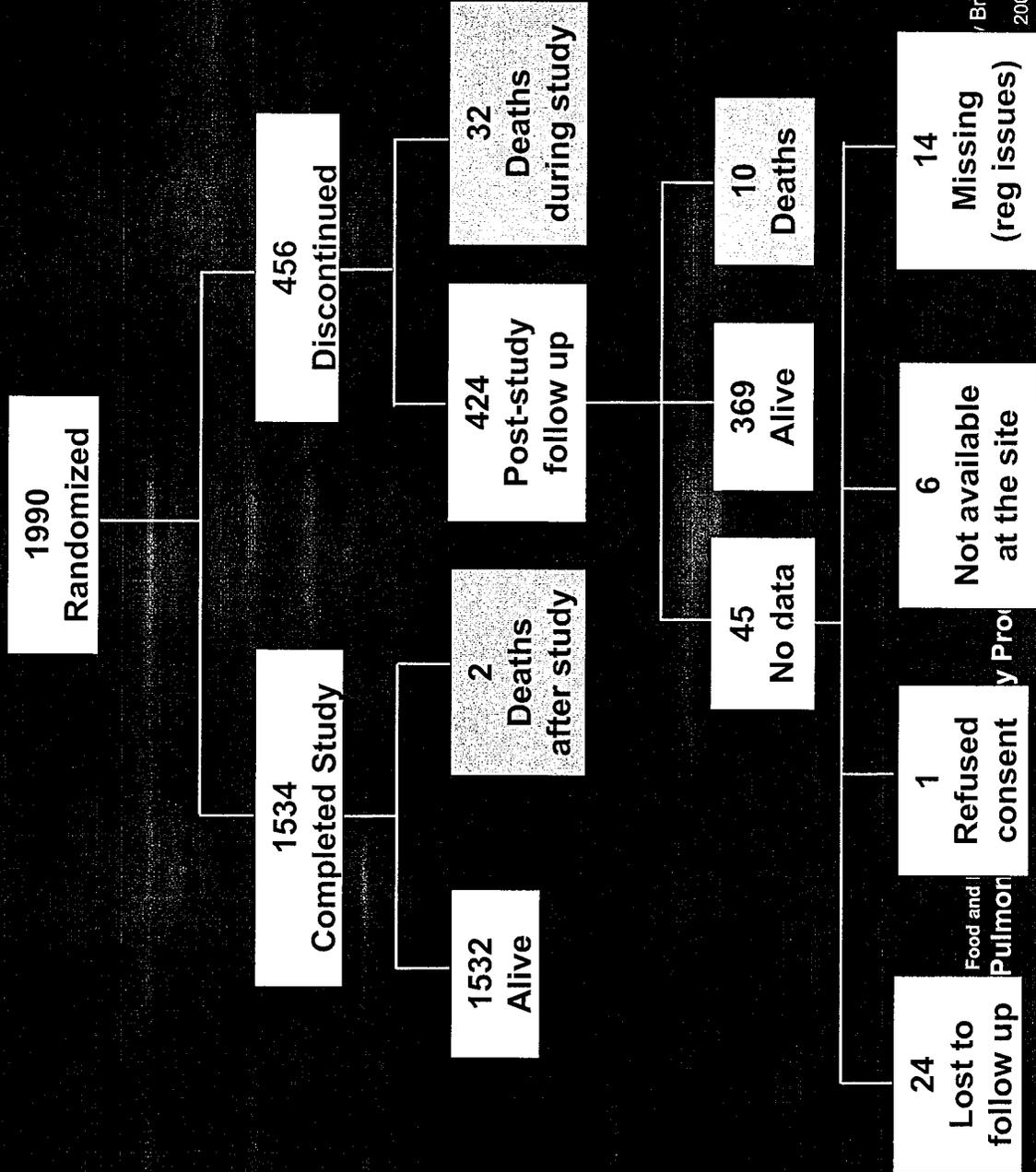
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Patient Disposition (Follow Up)



Vital Status Follow Up

	Placebo	Spiriva 5 mcg	Spiriva 10 mcg	Total
Study 254				
Enrolled	319	332	332	983
Completed	228 (72%)	277 (83%)	277 (83%)	782 (80%)
Vital Status Avail.	312 (98%)	328 (99%)	328 (99%)	968 (98%)
Study 255				
Enrolled	334	338	335	1007
Completed	220 (66%)	278 (82%)	254 (76%)	752 (75%)
Vital Status Avail.	323 (97%)	328 (97%)	326 (97%)	977 (97%)



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Number of Deaths

	205.254			205.255			Combined			
	tio R5	tio R10	plac	tio R5	tio R10	plac	tio R5	tio R10	plac	total
Original study reports	7	8	5	5	9	0	12	17	5	34
Worst case	9	8	7	7	11	2	16	19	9	44
Censored at 369 days	9	8	7	7	10	3	16	18	10	44
Best case	9	8	7	7	10	5	16	18	12	46



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Cause of Death (Worst Case)

Events leading to death	Tio R5 N=670	Tio R10 N=667	Placebo N=653
Total deaths	16	19	9
Cardiac failure	1	0	0
Myocardial infarction/coronary insufficiency	5	1	0
Gastrointestinal hemorrhage	0	1	1
Death (cause undetermined)	0	6	3
Neoplasms†	4	3	2
Motor vehicle accident	0	1	0
Suicide	1	0	0
Sepsis	0	1	0
CVA	0	1	1
COPD exacerbated	3	3	2
Pneumonia	2	2	0

†7 patients with lung, one esophageal, and one colon cancer



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Deaths Studies 254 and 255

Any Fatal Adverse Event	Placebo		5 mg Spiriva		10 mg Spiriva		5 mg Spiriva vs. Placebo		10 mg Spiriva vs. Placebo	
	# events (%) ¹	Relative Risk (95% C.I.) ²	Excess Incidence per 1000 pt years (95% C.I.) ³	Relative Risk (95% C.I.) ²	Excess Incidence per 1000 pt years (95% C.I.) ²					
Study 254										
Sample Size (baseline)	319	332	332	332	332	332				
Within Study	5 (1.9%)	7 (2.2%)	8 (2.4%)	8 (2.4%)	8 (2.4%)	8 (2.4%)	1.2 (0.4, 3.8)	3 (-20, 27)	1.4 (0.4, 4.2)	5 (-19, 28)
Retro Follow-up	7 (2.3%)	8 (2.5%)	8 (2.1%)	8 (2.1%)	8 (2.1%)	8 (2.1%)	1.1 (0.4, 3.0)	2 (-22, 26)	1.1 (0.4, 2.9)	-1 (-24, 21)
Study 255										
Sample Size (baseline)	334	338	338	338	335	335				
Within Study	0 (0.0%)	5 (1.6%)	8 (2.7%)	8 (2.7%)	8 (2.7%)	8 (2.7%)	undefined	16 (2, 30)*	undefined	27 (9, 46)*
Retro Follow-up	2 (0.6%)	7 (1.8%)	10 (2.8%)	10 (2.8%)	10 (2.8%)	10 (2.8%)	3.4 (0.7, 16.5)	12 (-5, 28)	5.0 (1.1, 22.9)*	21 (2, 41)*
Studies 254 & 255										
Sample Size (baseline)	653	670	670	670	667	667				
Within Study	5 (0.9%)	12 (1.9%)	16 (2.5%)	16 (2.5%)	16 (2.5%)	16 (2.5%)	2.1 (0.7, 5.9)	10 (-4, 23)	2.9 (1.1, 8.0)*	16 (1, 31)*
Retro Follow-up	9 (1.4%)	15 (2.1%)	18 (2.5%)	18 (2.5%)	18 (2.5%)	18 (2.5%)	1.6 (0.7, 3.6)	7 (-7, 21)	1.9 (0.9, 4.3)	10 (-5, 25)

1. Kaplan Meier estimates at 46 weeks.

2. As estimated by Cox proportional hazards regression with treatment as independent variable, stratified by study for pooled analyses.

3. As estimated by the difference in Kaplan Meier estimates at 46 weeks, expressed per 1000 person years.

* p<0.05



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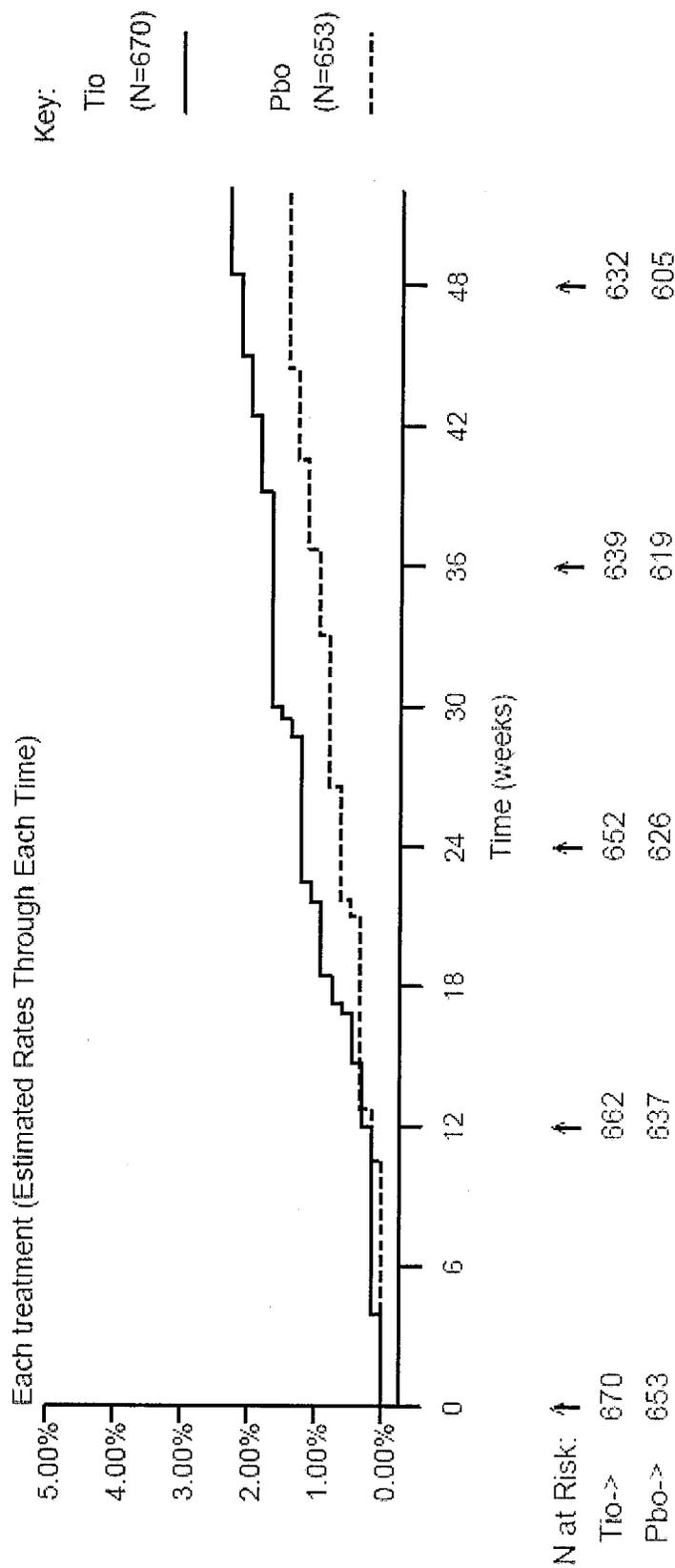
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Time to Death – Study 254 & 255

5 mcg Spiriva versus placebo

TIME TO FIRST OCCURRENCE OF EVENT (KAPLAN-MEIER Inference of 'If-Always-On-Treatment' Rates)



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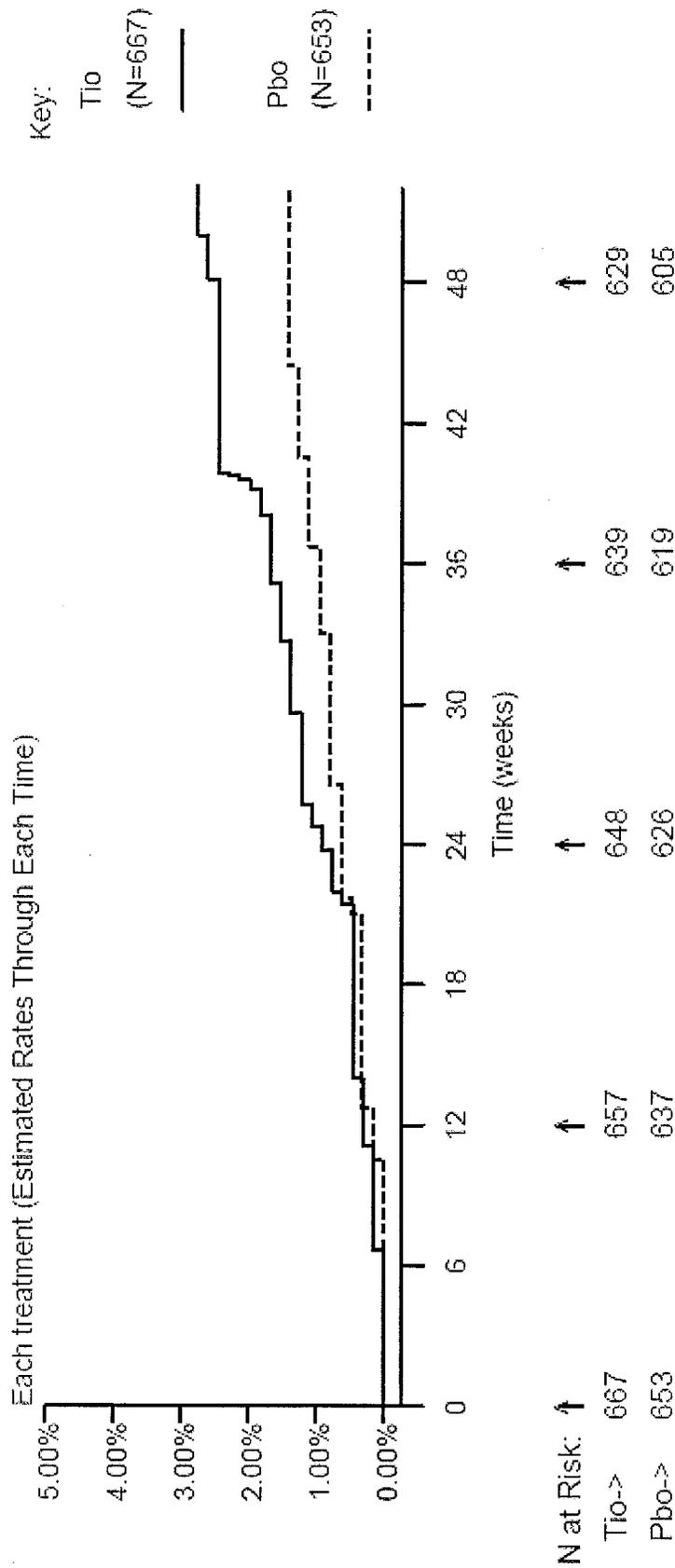
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Time to Death – Study 254 & 255

10 mcg Spiriva versus placebo

TIME TO FIRST OCCURRENCE OF EVENT (KAPLAN-MEIER Inference of 'If-Always-On-Treatment' Rates)



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Mortality by Country

- Deaths generally distributed evenly across countries when corrected for volume of enrollment
- Highest number of deaths
 - ◆ Russia: 9/205 (4.4%)
 - ◆ US: 7/316 (2.2%)
 - ◆ S Africa: 5/94 (5.3%)
- Deaths of unknown cause: 6 in Russia, 1 in US, 1 in France, and 1 in Italy



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Mortality Summary

- Potential explanations for signal
 - ◆ Differential drop outs
 - ◆ Real death signal
 - ◆ Other unknown confounder
- Death rate not unexpected for population
- No obvious other safety signal that could be linked to death
 - ◆ Cardiac (MI)
 - ◆ Pneumonia
- Nine deaths of unknown cause



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Conclusions

- Bronchodilator efficacy sufficient for approval demonstrated
- A portion of mortality signal can be explained by differential drop out
- Remainder of signal can not be explained with available data
- Further data needed to confirm safety



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Outline

- Introduction
 - ◆ Sally Seymour, M.D.
- Spiriva Respimat NDA and Mortality
 - ◆ Theresa Michele, M.D.
- Spiriva HandiHaler and Stroke
 - ◆ Banu Karimi-Shah, M.D.
- Questions for Discussion



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Spiriva HandiHaler

Risk of Stroke

- BI conducted analysis of safety data from 29 placebo-controlled clinical studies as a part of routine safety monitoring
 - ◆ 25 studies - Spiriva HandiHaler (tio 18 mcg)
 - ◆ 4 studies - Spiriva Respimat (tio 5 or 10 mcg)
 - ◆ 13,544 patients with COPD
 - 7856 patients – tiotropium
 - 5692 patients – placebo

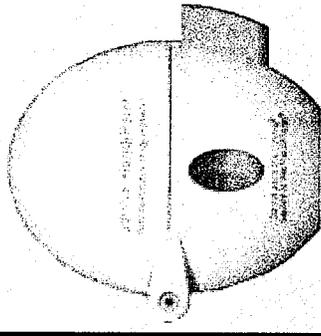


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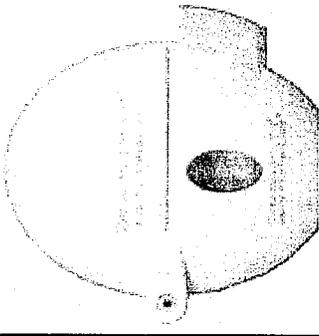
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Spiriva HandiHaler

Risk of Stroke



Incidence of Stroke in Spiriva HandiHaler and Spiriva Respimat Placebo Pooled Controlled Clinical Trials			
Incidence per 100 pt yr	Tiotropium	Placebo	RR (95% CI) Mantel Haenszel
Excess Incidence per 1000 pt yrs**			
HandiHaler and Respimat			
Any stroke event	31 (0.76)	15 (0.58)	1.37 (0.73, 2.56)
Serious*	30 (0.66)	14 (0.46)	1.62 (0.86, 3.08)
Fatal*	3 (0.07)	1 (0.03)	1.83 (0.25, 13.40)
HandiHaler			
Any stroke event	21 (0.77)	10 (0.50)	1.69 (0.77, 3.71)
Serious*	25 (0.77)	11 (0.44)	1.96 (0.94, 4.07)
Fatal*	2 (0.06)	0	
Respimat			
Any stroke event	10 (0.76)	5 (0.86)	0.87 (0.30, 2.56)
Serious	5 (0.38)	3 (0.51)	0.73 (0.17, 3.03)
Fatal	1 (0.08)	1 (0.17)	0.43 (0.03, 6.91)

* Includes data from Study 266

** Excess incidence was not provided and was estimated based upon the rate reported by the Sponsor.



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Early Communication

Early Communication about an Ongoing Safety Review of Tiotropium (marketed as Spiriva HandiHaler)

This information reflects FDA's current analysis of available data concerning this drug. Posting this information does not mean that FDA has concluded there is a causal relationship between the drug product and the emerging safety issue. Nor does it mean that FDA is advising health care professionals to discontinue prescribing this product. FDA is considering, but has not reached a conclusion about whether this information warrants any regulatory action. FDA intends to update this document when additional information or analyses become available.

The manufacturer of Spiriva HandiHaler, Boehringer Ingelheim, recently informed the FDA that ongoing safety monitoring has identified a possible increased risk of stroke in patients who take this medicine. Spiriva HandiHaler contains tiotropium bromide and is used to treat bronchospasm associated with chronic obstructive pulmonary disease (COPD). Additional information is needed to further evaluate this preliminary information about stroke in patients who take Spiriva HandiHaler.

Boehringer Ingelheim reported to the FDA that it has conducted an analysis of the safety data from 29 placebo controlled clinical studies ("pooled analysis"). In 25 of the clinical studies, patients were treated with Spiriva HandiHaler. In the other 4 clinical studies patients were treated with another formulation of tiotropium approved in Europe, Spiriva Respimat. The 29 clinical studies included approximately 13,500 patients with COPD. Based on data from these studies, the preliminary estimates of the risk of stroke are 8 patients per 1000 patients treated for one year with Spiriva, and 6 patients per 1000 patients treated for one year with placebo. This means that the estimated excess risk of any type of stroke due to Spiriva is 2 patients for each 1000 patients using Spiriva over a one year period.

It is important to interpret these preliminary results with caution. FDA has not confirmed these analyses. Pooled analyses can provide early information about potential safety issues. However, these analyses have inherent limitations and uncertainty that require further investigation using other data sources. This early communication is in keeping with FDA's commitment to inform the public about its ongoing safety reviews of drugs.



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Tiotropium Planned Stroke

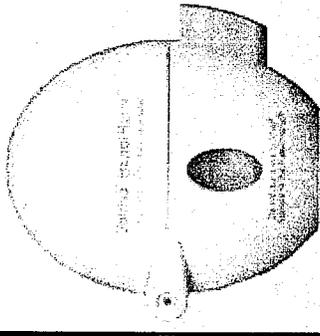
Analysis

- Verify BI's pooled analysis
- Requested data and narratives from BI
 - ◆ Strokes
 - Expanded MedDRA query
 - ◆ Fatal adverse events
- VA study
 - ◆ ipratropium and tiotropium and strokes
- UPLIFT results



UPLIFT

- Understanding Potential Long-term Impacts on Function with Tiotropium
- Randomized, Double-Blind, Placebo Controlled 4 Year
 - ◆ 6000 patients with COPD
 - ◆ Tiotropium HandiHaler vs. placebo
- Objective
 - ◆ Effect of tiotropium on rate of decline of FEV₁ - disease progression
- Efficacy
 - ◆ 1° EP - yearly rate of decline in trough and 90 min FEV₁
 - ◆ 2° EP includes COPD exacerbations



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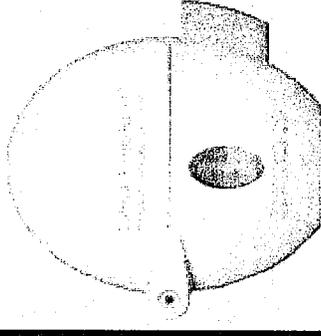
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UPLIFT

- Safety analysis
 - ◆ AEs
 - ◆ SAEs (including strokes)
 - ◆ Fatal adverse events
- Amendments to address mortality
 - ◆ Vital status (including cause of death) collected every 6 months for each prematurely discontinued patient
 - ◆ Two step adjudication process for all deaths



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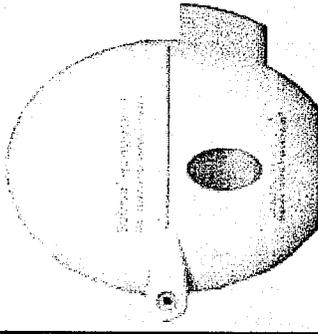


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UPLIFT Preliminary Results

Stroke

- 5,993 patients randomized
- 162 patients with stroke
 - ◆ 82 tiotropium
 - ◆ 80 placebo



	Rate Ratio (Tio/Pbo)
All Stroke Events	0.95 [0.70 – 1.39]
Serious Stroke Events	0.98 [0.70 – 1.39]
On-treatment Fatal Strokes	0.92 [0.41 – 2.05]
On-treatment Fatal Strokes (adjudicated)	0.85 [0.39 – 1.87]
Vital Status Follow-Up	0.82 [0.40 – 1.66]



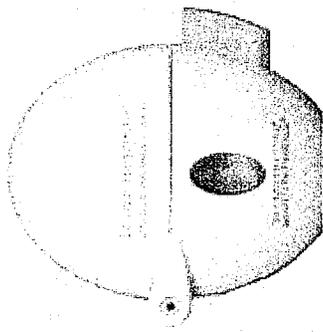
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UPLIFT Preliminary Results

Mortality



	Placebo	Tiotropium 18 mcg	Total
		N	
		(%)	
Total Treated	3006	2986	5992
Total Deaths (on treatment)	410 (13.6)	381 (12.8)	791 (13.2)
Total Deaths (including discontinued patients)	514 (17.1)	467 (15.6)	981 (16.4)



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Summary

- Pooled analysis of 29 clinical trials revealed potential signal for increased stroke risk in patients treated with tiotropium
- UPLIFT data (per Sponsor's analysis) suggests that there is not an increased risk of stroke
- Await official submission of UPLIFT to review data regarding stroke and mortality



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Outline

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 - ◆ Theresa Michele, M.D.
- Spiriva HandiHaler and Stroke
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- Questions for Discussion



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Summary

- Spiriva HandiHaler
 - ◆ Pooled clinical trial data suggested increased risk of stroke
 - ◆ Preliminary data from UPLIFT suggests no increased risk of stroke with Spiriva HandiHaler

- Spiriva Respimat NDA
 - ◆ Efficacy data sufficient for approval
 - ◆ Mortality imbalance cannot be completely explained
 - ◆ No evidence of increased risk of stroke

- UPLIFT results available soon to provide long term safety data with Spiriva HandiHaler

- Plan to take NA action on Spiriva Respimat NDA and await UPLIFT data to provide more information about mortality and stroke with tiotropium bromide



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Revised Questions

- Given the preliminary UPLIFT data regarding mortality and stroke, DPAP now plans to take an AP action on the Spiriva Respimat NDA.

Does the committee have comments regarding this approach?



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Revised Questions

- What are the committee's thoughts on the mortality data?
- What are the committee's thoughts on the stroke data?



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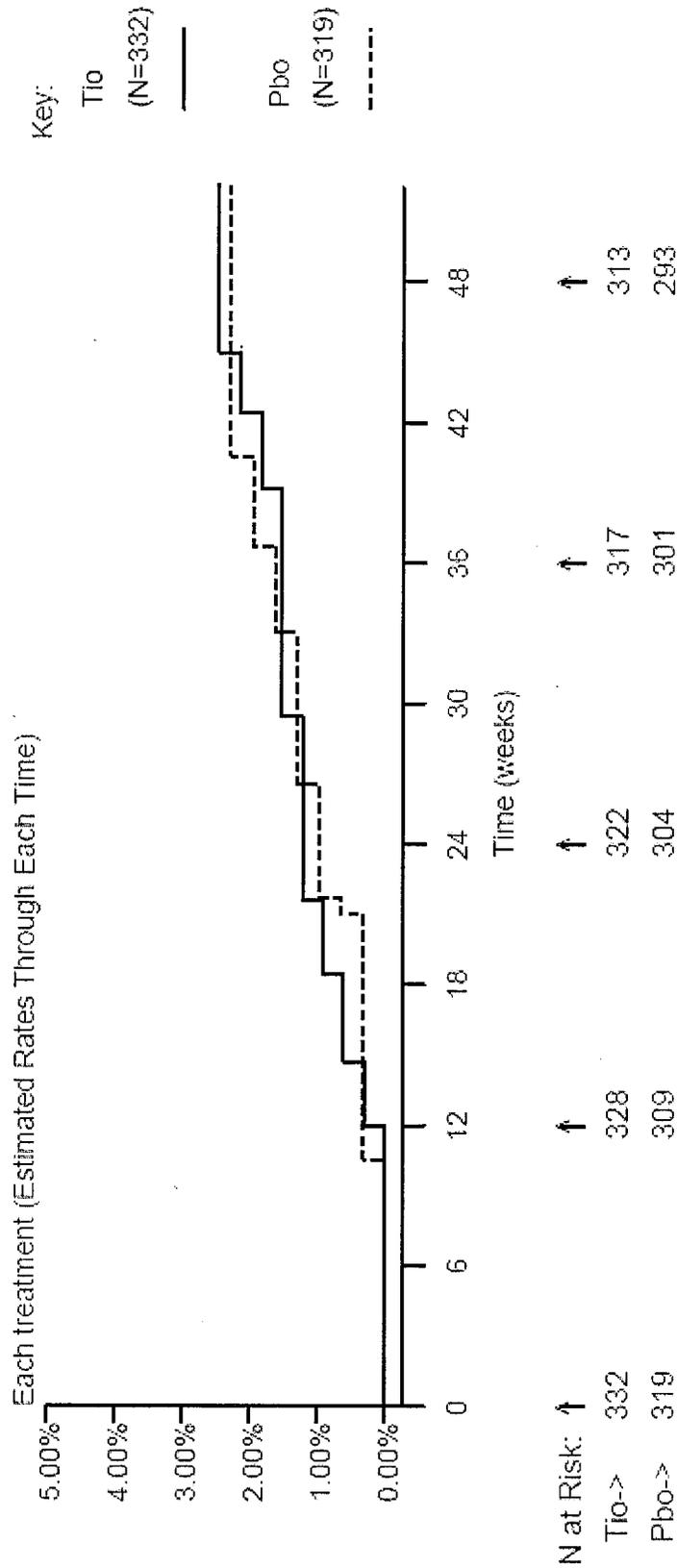
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Time to Death – Study 254

5 mg Spiriva versus placebo

TIME TO FIRST OCCURRENCE OF EVENT (KAPLAN-MEIER Inference of 'If-Always-On-Treatment' Rates)



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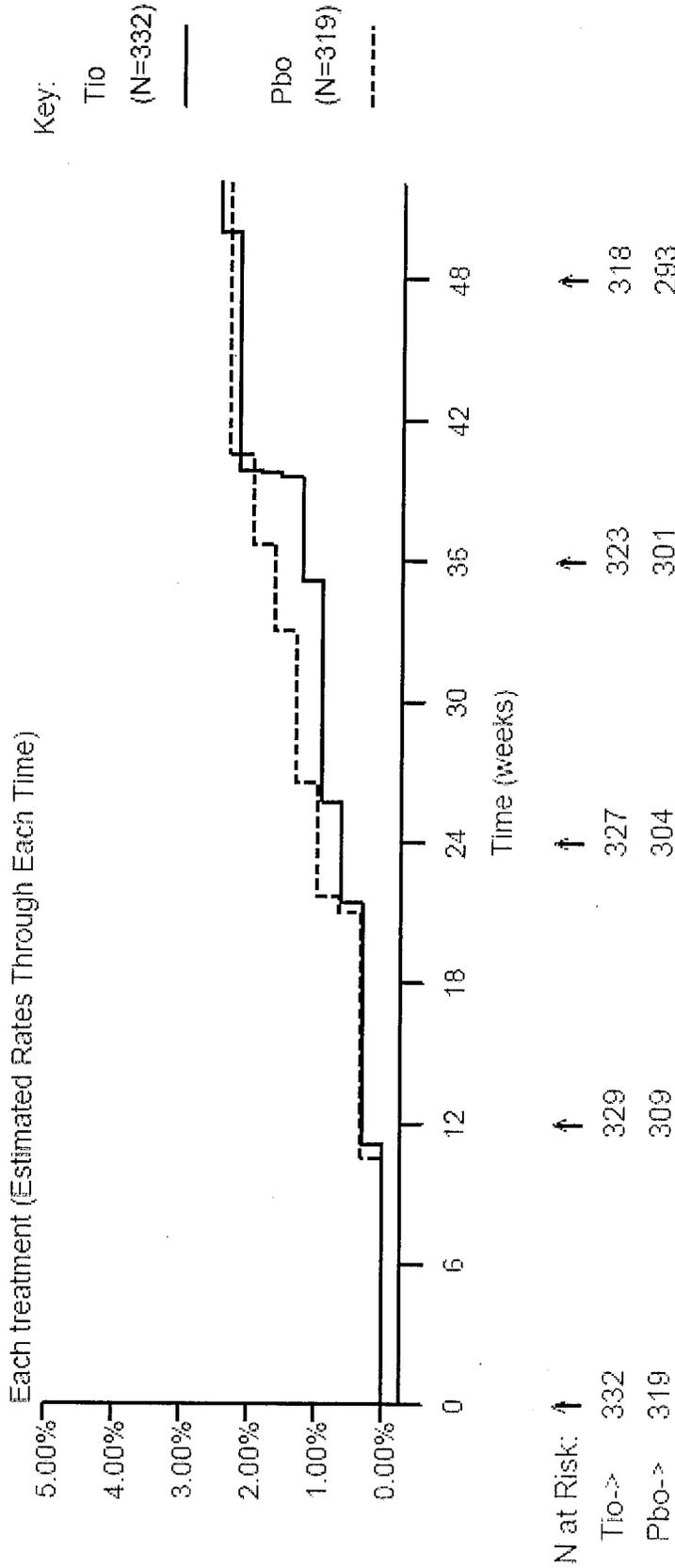


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Time to Death – Study 254

10 mcg Spiriva versus placebo

TIME TO FIRST OCCURRENCE OF EVENT (KAPLAN-MEIER Inference of 'If-Always-On-Treatment' Rates)



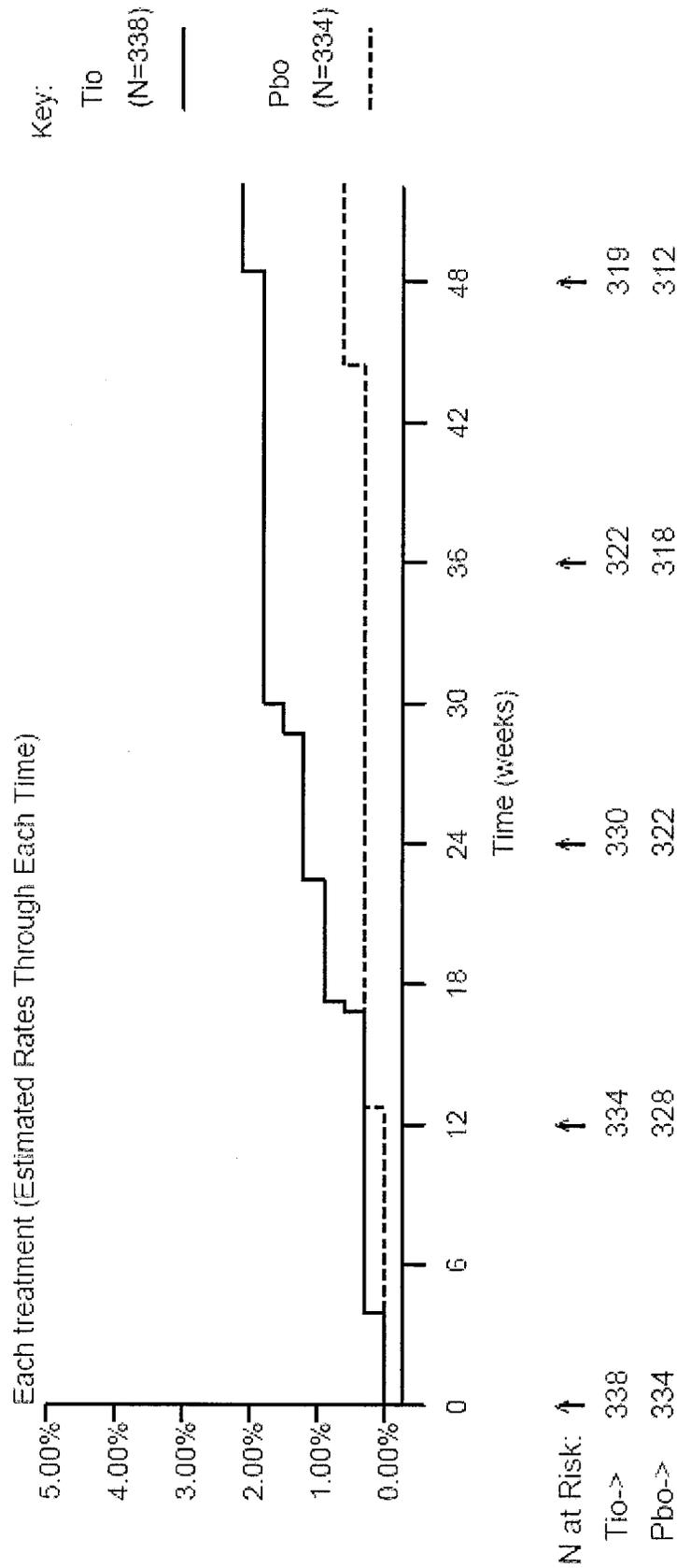
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Time to Death – Study 255

5 mcg Spiriva versus placebo

TIME TO FIRST OCCURRENCE OF EVENT (KAPLAN-MEIER Inference of 'If-Always-On-Treatment' Rates)



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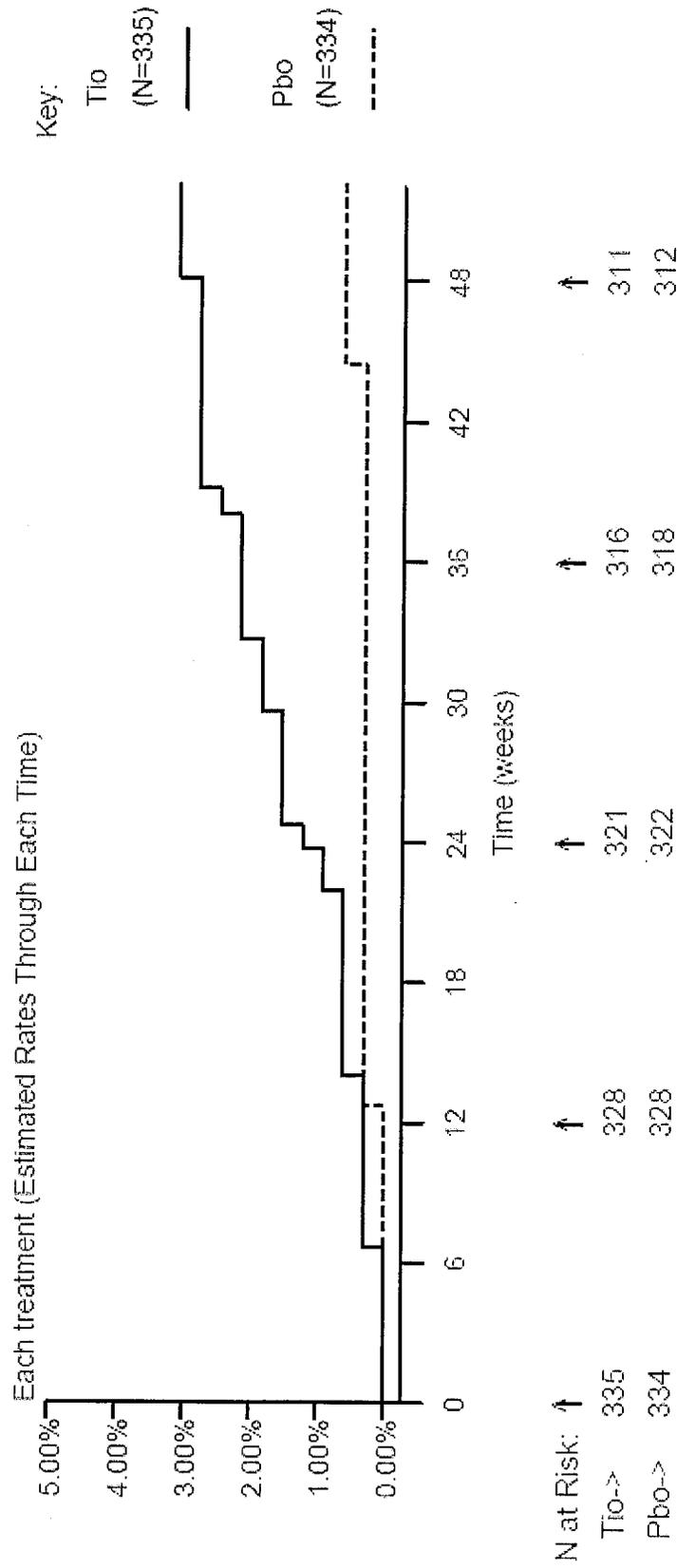


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Time to Death – Study 255

10 mcg Spiriva versus placebo

TIME TO FIRST OCCURRENCE OF EVENT (KAPLAN-MEIER Inference of 'If-Always-On-Treatment' Rates)



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1/29/08

APPEARS THIS WAY ON
ORIGINAL

NDA 21-936 (Spiriva Respimat) Filing Meeting

Prasad Peri
ONDQA
DPA1



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Spiriva Respimat Filing Meeting

1/29/2008

Drug Substance

- Tiotropium Bromide is an approved drug substance made by BI and is referenced to DMF 18135. The DMF describes two qualities of drug substance one for powder and one for inhalation solutions.
- The inh. soln. quality contains microbial specification and does not have control for PSD.
- Solubility is (b) (4)
- Microbial data over 24 months are presented. Retest period is (b) (4) years.
- Impurities are controlled fairly tightly. Total of all impurities \leq (b) (4).



Drug Substance

Chromatographic purity	(b) (4)		HPLC
	Every other unspecified impurity	(b) (4)	
	Total of all impurities	(b) (4)	TLC

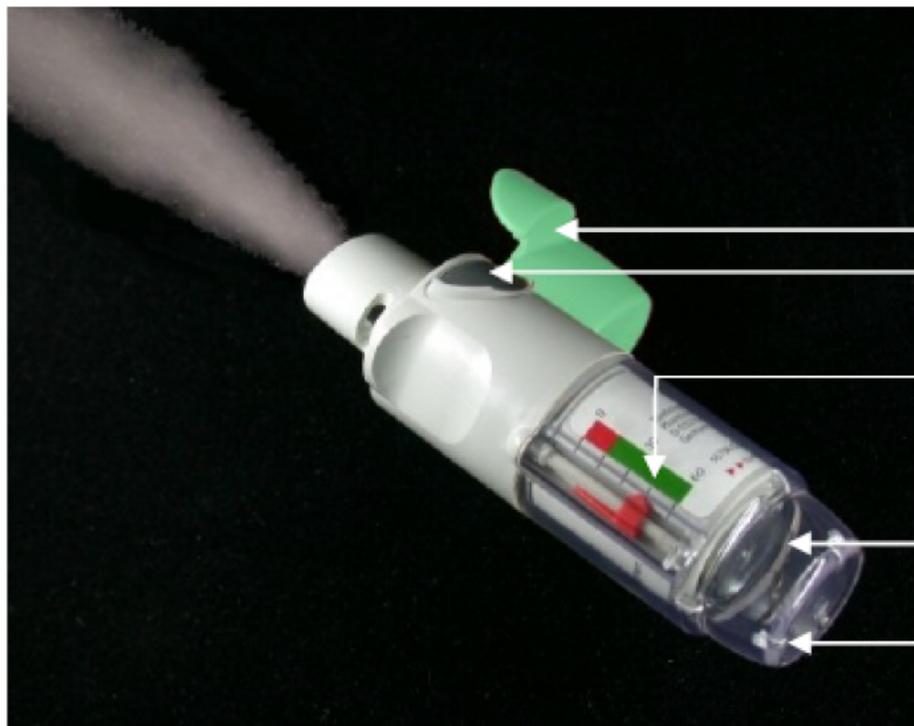
Microbiological Purity	Total viable aerobic count	(b) (4)	Microbiological determination in accordance with USP
	(b) (4)		



Drug Substance

(b) (4) (used in Phase II clinical trial supplies of Spiriva® Respimat®)	(b) (4) (used in stability studies)
(b) (4) (used in Phase III clinical trial supplies of Spiriva® Respimat®)	(b) (4) (used in stability studies)
(b) (4) (used in Phase III clinical trial supplies of Spiriva® Respimat®)	(b) (4) (used in stability studies)
(b) (4) (used in stability studies)	(b) (4) (used in stability studies)
(b) (4) (used in stability studies)	(b) (4) (used in stability studies)
(b) (4) (used in stability studies)	(b) (4) (used in stability studies)





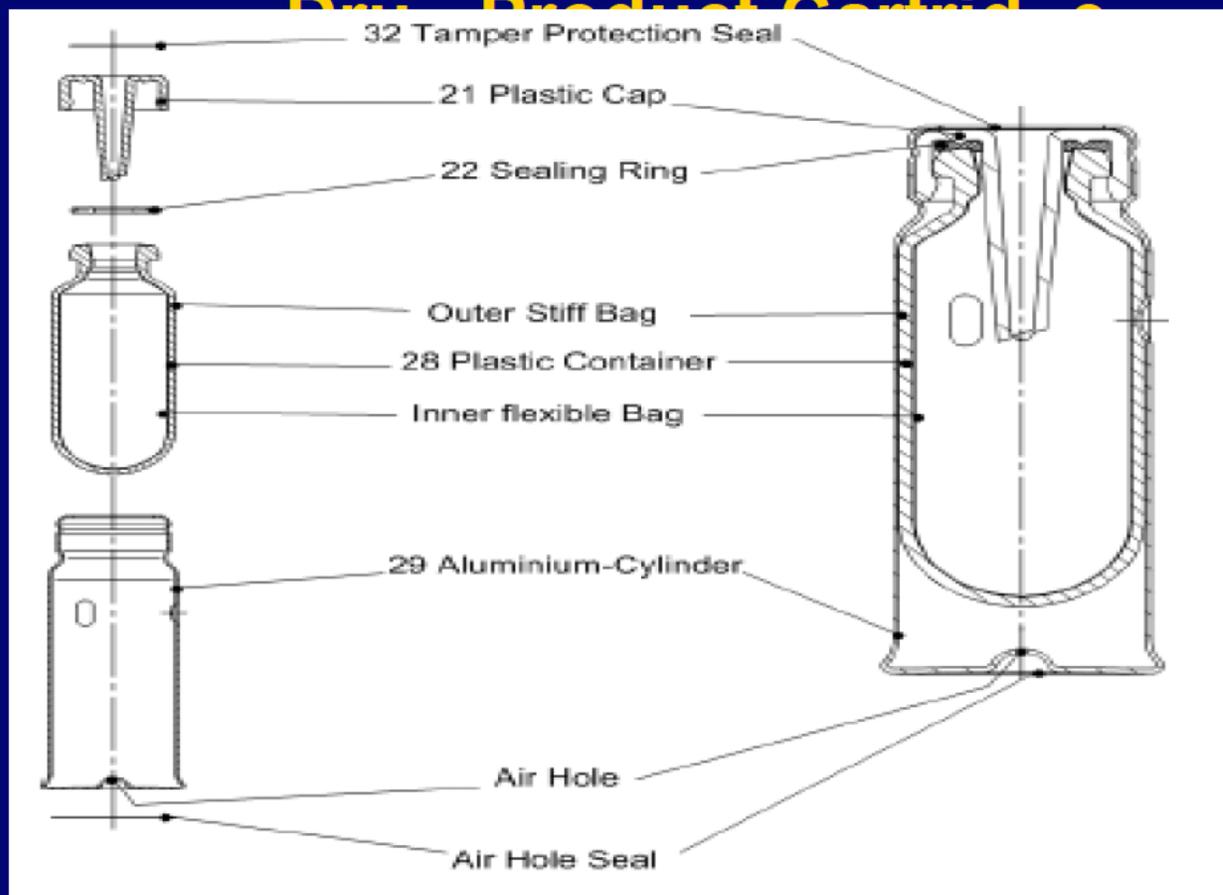
cap
trigger
dose indicator
bottom of inserted cartridge
transparent lower part



Figure 5: Patient inhaling Spiriva® Respimat®



Drug Product Cartridge



The cartridge contains a minimum fill of 4 ml. As the declared number of 30 doses of (b) (4) each (metered volume) corresponds to about (b) (4) the cartridge comprises an overfill of approximately (b) (4)

Overfills are common to multi-dose inhalation products. The Respimat[®] overfill is required for proper container functionality. The locking mechanism of the Respimat[®] inhaler guarantees that the overfill cannot be extracted from the cartridge. Therefore, the overfill is, in contrast to pMDIs, not accessible to the patient.

Drug Product Formulation

Name of Ingredient	Function	Reference to Standards	Per dose ¹ (Label Claim) (mg)	Percentage Formula (g/100ml)	Per cartridge ⁴ (mg)
Tiotropium ²			0.005		(b) (4)
corresponds to Tiotropium bromide monohydrate	Drug substance	In house standard			(b) (4)
Benzalkonium chloride ³	Preservative	NF			
Edetate Disodium	Stabilizer	USP			
1 N Hydrochloric acid	pH-Adjustment	NF			
Water for injection	Solvent	USP			
Nitrogen	Gas for filtration	NF			
Total weight			22.1	100.0	(b) (4)

¹ One dose consists of two actuations.

² The declaration refers to Tiotropium (tiotropium cation) as the active moiety in tiotropium bromide monohydrate.

(b) (4)

³ The declared amount of benzalkonium chloride refers to the anhydrous substance.

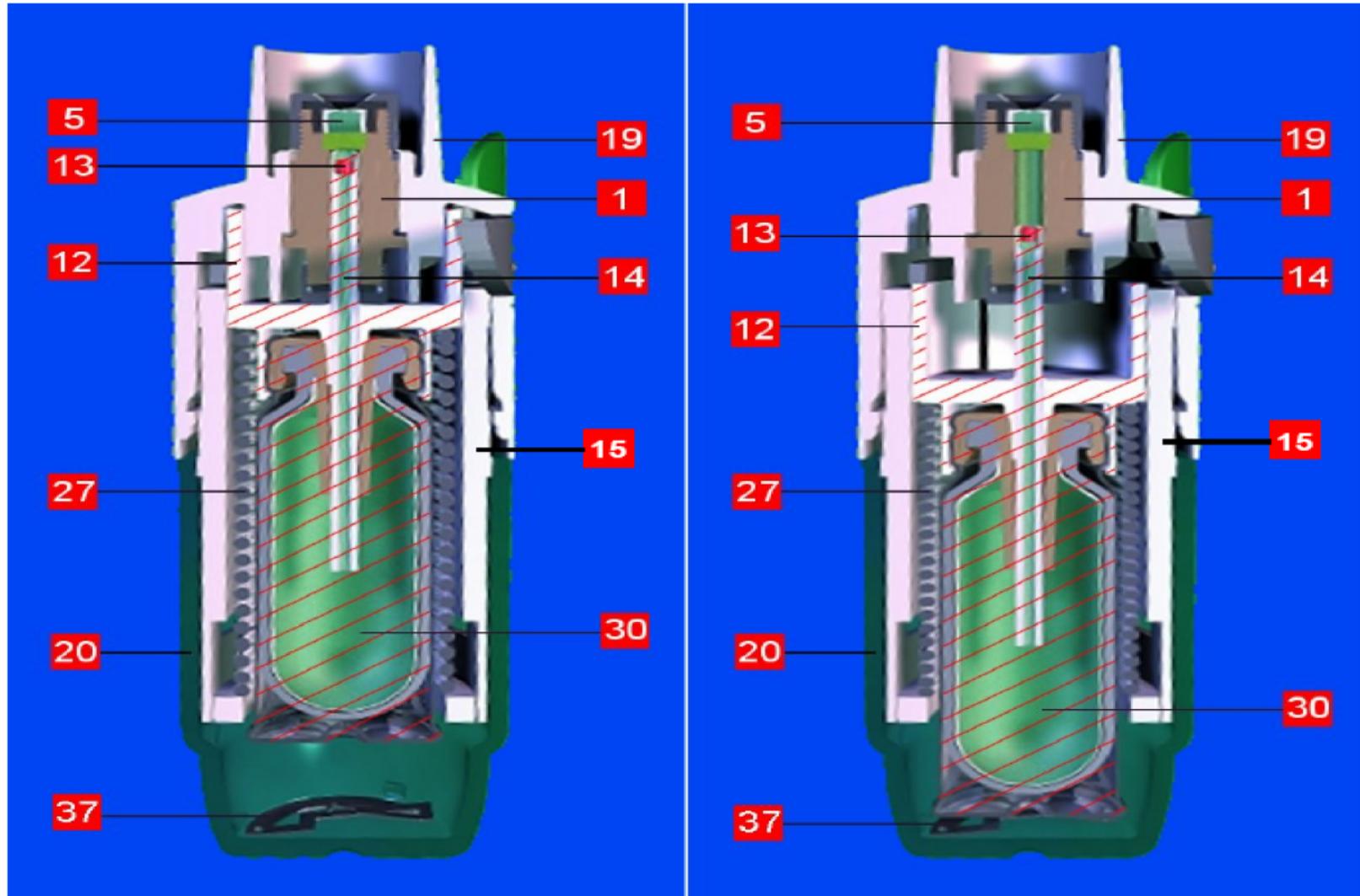
⁴ This composition statement refers to a nominal filling volume (b) (4) per cartridge. This target filling volume comprises the amount of solution which corresponds to the labeled number of 30 doses plus a technically required overfill.

Table 6: Metered and delivered volume of Spiriva® Respimat®

Metered and delivered volume of Spiriva® Respimat®	Volume per dose
Metered volume (<i>ex valve</i>)	(b) (4)
Delivered volume (<i>ex mouthpiece</i>)	22.1 µl

Drug Product Device

ATTACHMENT 6: CROSS SECTION SHOWING THE FUNCTION OF THE RESPIMAT® INHALER



After actuation
Capillary in upper position

Prior to actuation
Capillary in lower position

Drug Product Changes

Cartridge design: Phase III supplies had used (b) (4). Due to a discontinuation of supply, the commercial product will use another (b) (4) type, (b) (4)

subjected to a sterilization with ethylene oxide. The changes did not influence the properties of the product, as indicated by unchanged batch release and stability data. For a tabular presentation, please refer to Attachment 3, page 68 *seqq.*

- the Respimat[®] version A4 – it has been used in the Phase III clinical studies (Study nos. 205.249, 205.250, 205.251, 205.252, 205.254, and 205.255), which demonstrate the safety and efficacy and serve as basis for the dose selection (see CTD Module 2.5: Clinical Overview), and in supportive stability studies
- the Respimat[®] version A5, which is intended for the commercial product; it has been used in primary stability studies



Drug Product Changes

The key development step from Respimat[®] A4 to Respimat[®] A5 was the inclusion of a locking mechanism to lock the Respimat[®] A5 after 30 doses. Further changes between the two versions are merely cosmetic (*e.g.*, change in cap color). Neither unblock nor the cartridge system nor the composition of the solution was changed.

The locking mechanism does not interfere with the dosing and nebulization before locking. Table 7 demonstrates the equivalence of the two versions of the device by comparing *in vitro* performance data of product batches.

	Clinical supply for Phase III study	Product in market configuration
Respimat [®] type used	Respimat [®] A4	Respimat [®] A5
Batch no. solution / Respimat [®] inhaler	<i>e.g.</i> : 202820 / WE 01070189	<i>e.g.</i> : 405441 / 3U0024
Target delivered dose [μg]	5	5
Delivered dose [μg] *	(b) (4)	
Aerodynamic particle size distribution by ACI [% of target dose in Group 1 / 2 / 3]		
Aerodynamic particle size distribution by Laser [% of particles in Group 1 / 2 / 3]		

* Delivered dose values for Batch 202820 / WE 01070189 were determined according to the draft FDA Guidance “Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products”; for batch 405441 / 3U0024, they are given as start (S) and end (E) values of the spray content uniformity test.



Drug Product Batches

* : long-term storage (25°C / 60%), 3 and 6 months data also after accelerated storage (40°C / 75%)

Set	Cartridge and Respimat® inhaler batch nos.	inhaler version	composition	batch size (kg)	use of batch	(b) (4)	stability data reported (months) *	Stability report nos.	Remark	
1 st	202820 / WE01070189	A4	identical	(b) (4)	phase III clinical supply (study 205.254); stability batch	[REDACTED]	0, 3, 6, 9, 12, 18, 24, 36	solution parameters: H011185	---	
	202820 / WE01080199				phase III clinical supply (studies 205.249, 205.250, 205.255)		0, 3, 6, 9, 12, 18, 24, 36 (cartridge)		---	
	202948 / WE01070187				phase III clinical supply (studies 205.251, 205.252); stability batch		0, 3, 6, 9, 12, 18, 24, 36		performance parameters: H011186	Executed batch record provided
	204543 / WE01070188				Stability batch		0, 3, 6, 9, 12, 18, 24, 36		---	
3 rd	405441 / 3U0024	A5	identical	(b) (4)	Primary stability batch	[REDACTED]	0, 3, 6, 9, 12, 18, 24	H012912	---	
	405766 / 3U0025				Primary stability batch		0, 3, 6, 9, 12, 18, 24		---	
	405792 / 3U0026				Primary stability batch		0, 3, 6, 9, 12, 18, 24		Executed batch record provided	



Drug Product Characterization Studies

- A) Priming / Repriming in Various Orientations / Effect of Resting Time
- B) Temperature Cycling
- C) Cleaning Instructions
- D) Device Robustness
- E) Effect of Dosing Orientation
- F) Tail Off Characteristics
- G) Plume geometry
- H) Preservative Effectiveness and Sterility Maintenance
- I) Stability of Primary (Unprotected) Package
- J) Characterization of Individual Actuations



Drug Product Characterization Studies

- B) **Temperature Cycling**
A 4-week temperature cycling [REDACTED] ^{(b) (4)} had no effect either on the unopened cartridge or on the inhaler with cartridge inserted.
- C) **Cleaning Instructions**
Delivered dose and particle size distribution data support the cleaning instruction as presented in the patient leaflet “Clean at least once a week”.
- D) **Device Robustness**
The Respimat[®] inhaler is robust and not harmed by being dropped or by vibrations.
- E) **Effect of Dosing Orientation**
The orientation during actuation does not influence the inhaler performance.



Drug Product Characterization Studies

- F) Tail Off Characteristics
Neither delivered dose nor particle size distribution change after the labeled number of 30 doses up to 60 doses. The study was performed on the Respimat[®] A4 inhaler, *i.e.* without locking mechanism.
- G) Plume geometry
The plume of Spiriva[®] Respimat[®] Inhalation Spray is of conical shape.
- H) Preservative Effectiveness and Sterility Maintenance
Please refer to the discussion in the section “Microbiological status”, page 35.
- I) Stability of Primary (Unprotected) Package
For Spiriva[®] Respimat[®], the term “primary (unprotected) package” means the cartridge inserted into the inhaler, with air hole seal, tamper protection seal and cap pierced.
Stability studies on chemical, microbiological and performance parameters (*cf.* Section 2.3.P.8) demonstrate that the product remains stable in this state for at least 3 months.
- J) Characterization of Individual Actuations
One dose of Spiriva[®] Respimat[®] consists of two actuations. Data on delivered dose and particle size distribution on individual actuations show equivalent results for the first and second actuation.



Drug Product Performance-APSD

(b) (4)



Drug Product Performance-APSD



Drug Product CQA

2.3.P.2.5.2 Critical quality attributes of the drug product

The Development Pharmaceuticals discusses the following attributes:

1. Delivered dose: Which factors influence the delivered dose? Which controls are in place? What are in-use mode and sequential mode of actuation? Is the delivered dose consistent over the content of the cartridge and during shelf-life?
2. Particle size distribution: Which factors influence the distribution? Which controls are in place? Is the distribution consistent over the content of the cartridge and during shelf-life?
3. Microbiological status
4. Functionality during patient use
5. Extractables and leachables



Drug Product CQA

Study	Total viable aerobic count [cfu / ml]	Remark
Inhalers used in laboratory environment for 1 and 3 months	Sampling after 1 month's use: 1 out of 18 samples: (b) (4) all other samples: (b) (4) (LoD) Sampling after 3 months' use: 3 out of 36 samples: (b) (4) all other samples: (b) (4) (LoD)	- - -
Inhalers returned from Phase III Clinical Trials 205.249, 205.251, 205.252, 205.254, 205.255	19 out of 205 samples: max. (b) (4) 186 out of 205 samples: (b) (4) (LoD)	Predominant species: (b) (4) (8 samples) (b) (4) (3 samples)

In conclusion, for the unopened Spiriva[®] Respimat[®] cartridge, sterility is guaranteed. Spiriva[®] Respimat[®] has been designed to fulfill FDA's requirements for an appropriate microbiological quality during use.



Drug Product CQA

Table 11: Results of performance testing of returned Respimat® A4 inhalers: Delivered dose and Aerodynamic particle size distribution (b) (4), batch 202948 / WE01070187. MV: mean value, IV: individual values

Test Parameter		Results of testing of returned inhalers [% target]	Results of batch release testing [% target]
Delivered dose [target: 5 µg]		MV (b) (4) IV: (b) (4)	MV (b) (4) IV: (b) (4)
Aerodynamic particle size distribution	Group 1	MV (b) (4)	MV (b) (4)
	Group 2	MV (b) (4)	MV (b) (4)
	Group 3	MV (b) (4)	MV (b) (4)

The Spiriva® clinical phase III studies used about 14,000 inhalers. Only 13 relevant malfunctioning inhalers could be confirmed. In 10 of these 13 cases the cartridge did not contain enough solution to deliver the doses. The other three complaints were caused by assembly errors or individual failure. Corrective actions have been implemented to prevent the defects with future batches.

In the Berodual® study, no malfunctioning inhalers at all were reported out of approx. 250 inhalers used.



Drug Product Degradation

(b) (4)

Special attention is drawn to the following justifications:

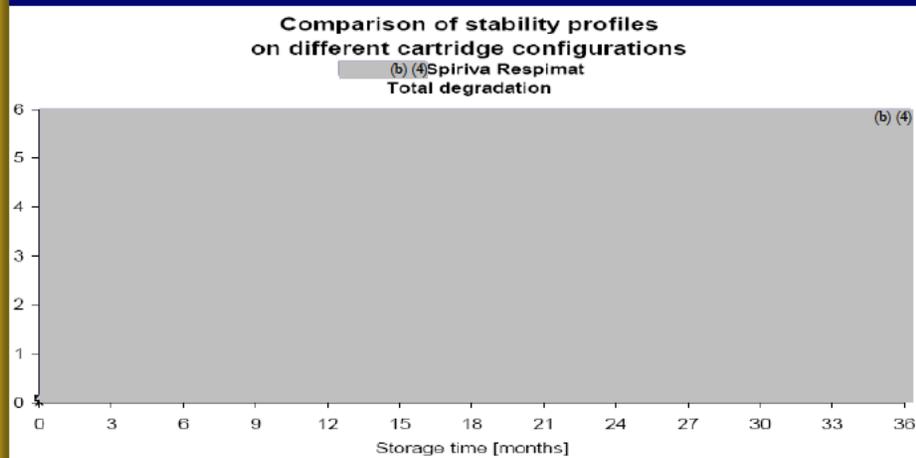
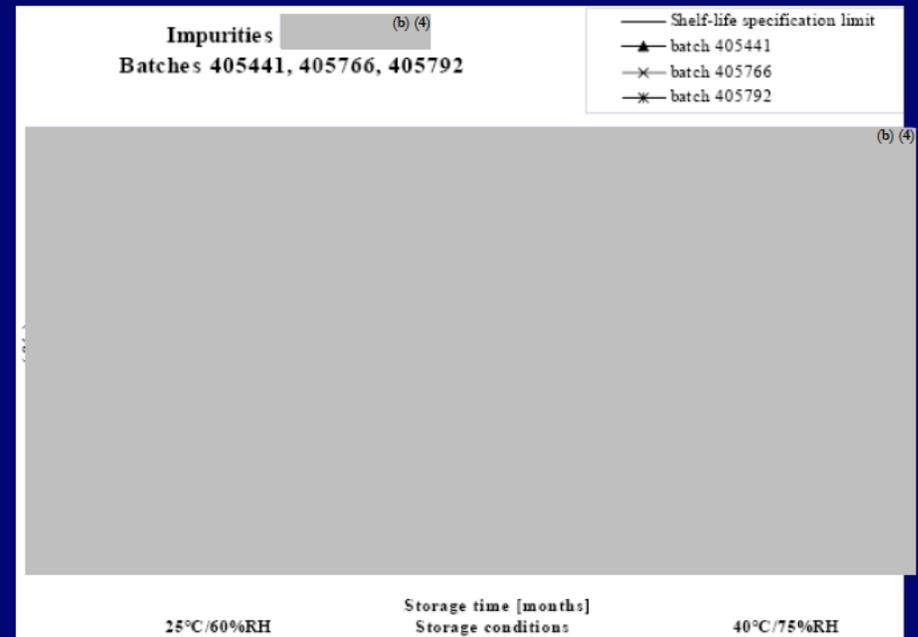
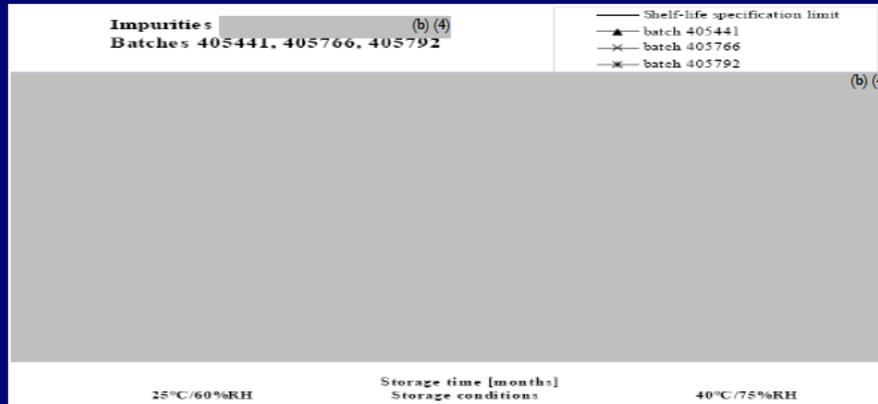
1) Active ingredient degradation:

The proposed acceptance criteria were derived from development data, from 36-months' long-term storage data and follow the ICH approach (one-sided 95 % confidence interval).

The proposed specification limits for the individual degradation products do not raise any toxicological concerns (*cf.* Non-Clinical Overview, chapter "Impurities, degradation products and packaging materials").

Drug Product Proposed limits

Test Parameter	Acceptance Criteria	Test Method	Analytical procedure no.
Impurities:	(b) (4)	HPLC, HPLC-MS (for (b) (4))	020192 (HPLC) 020538 (HPLC-MS)
Any unidentified degradation product	(b) (4)		
Sum of all degradation products	(b) (4)		



Drug Product Extractables and Leachables

The **extractable** profile of the primary cartridge parts has been investigated with three solvents of different polarities. Whereas aqueous extraction did not reveal any meaningful extractives from any of the polymers, organic extraction gave the following key extractables consistently among the polymer batches (see also Table 16, page 60):

- Antioxidants, [REDACTED] (b) (4)
- Oligomers, [REDACTED] (b) (4)

The purity profile of the aluminium cylinder with air hole seal as secondary protective packaging material has been investigated: No volatiles above [REDACTED] (b) (4) were found.

Leachables data have been generated by long-term stability studies. In the stability set representing the commercial product (“3rd set”, see Section 2.3.P.8), leachables were found only in levels below [REDACTED] (b) (4). They were identified [REDACTED] (b) (4). The levels are clearly below the Safety Concern Threshold [REDACTED] (b) (4) set in the PQRI working group 2006 recommendations. This demonstrates that no meaningful amounts of leachables migrate into the formulation; the result is consistent with the known low solubility of the extractables in aqueous systems.



Drug Product DMFs

DMF no.	DMF Holder	Content
Component DMFs:		
17322	Boehringer Ingelheim microParts (BImP)	Respimat [®] inhaler
17403	BImP	Plastic cap with integrated sealing ring
		(b) (4)
(b) (4)		



Drug Product-SCU Stability

Spray content uniformity data

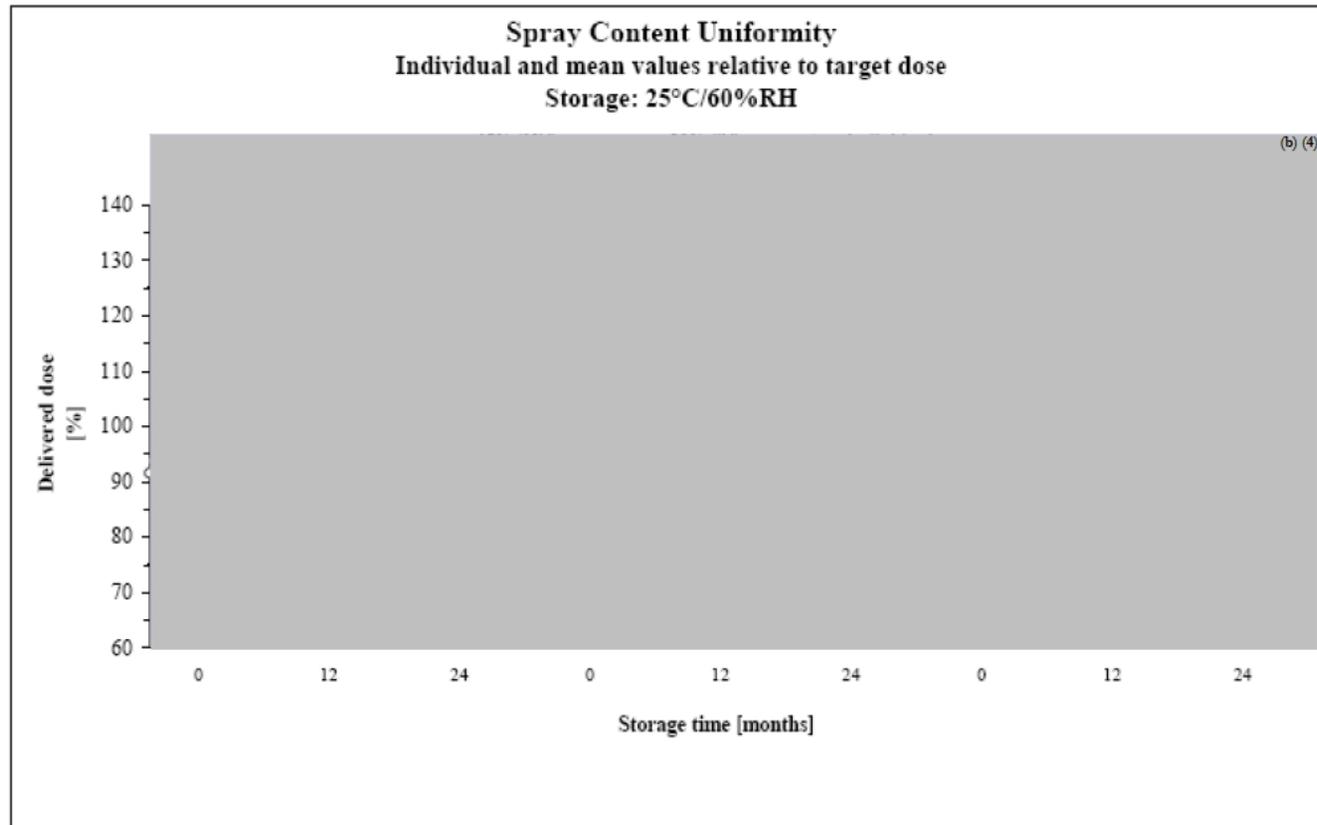
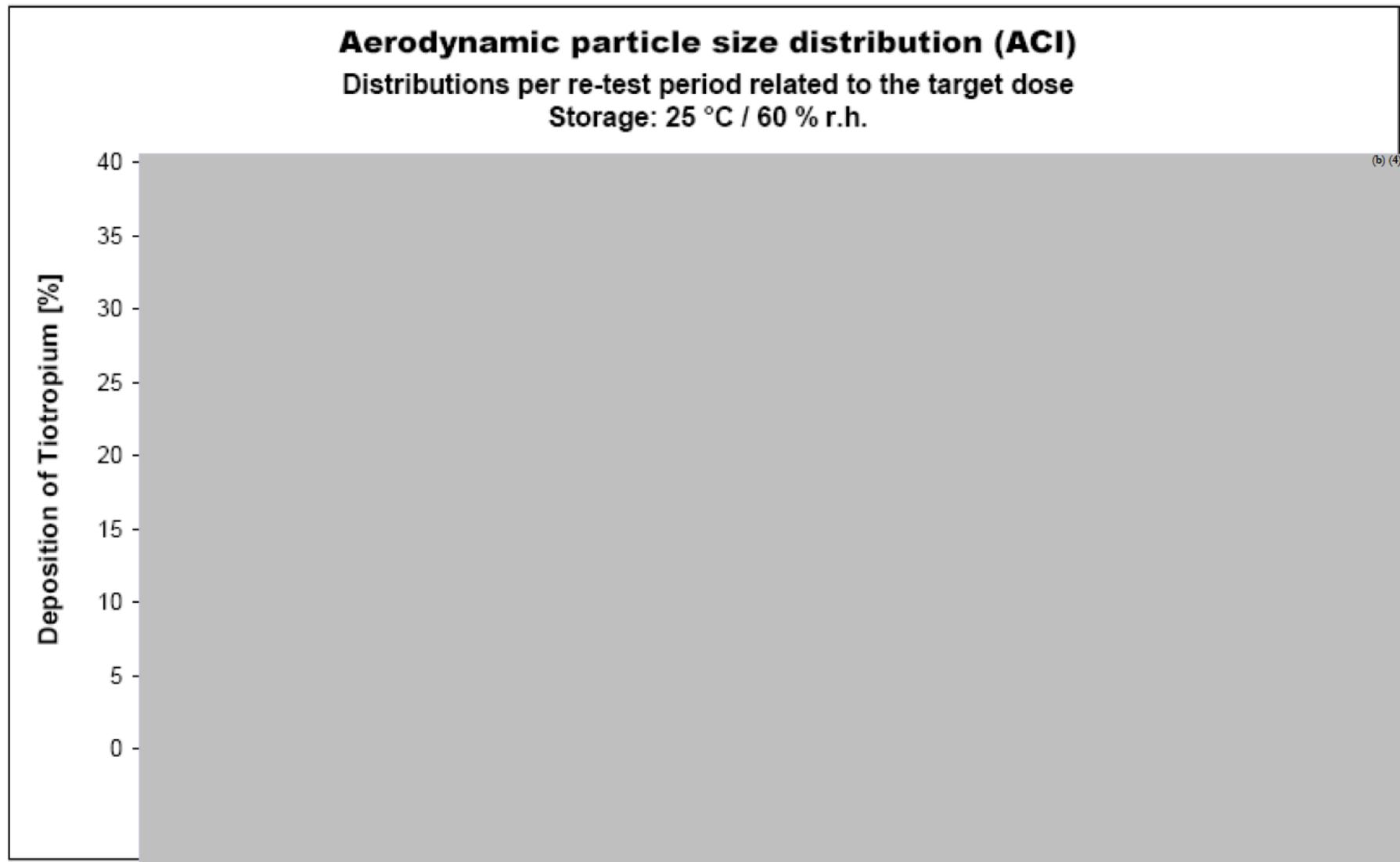


Figure 20: Spray content uniformity data of the three stability batches of the 3rd set over 24 months at 25°C / 60% r.h. Both individual values (open circles) and mean values (lines) are shown.



Drug Product-APSD Stability

Aerodynamic particle size distribution data (ACI):



Drug Product-Filing List

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	X		
2	Is the section indexed and paginated adequately?	X		
3	On its face, is the section legible?	X		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	X		
5	Is a statement provided that all facilities are ready for GMP inspection?	X		
6	Has an environmental assessment report or categorical exclusion been provided?	X		
7	Does the section contain controls for the drug substance?	X		
8	Does the section contain controls for the drug product?	X		
9	Have stability data and analysis been provided to support the requested expiration date?	X		



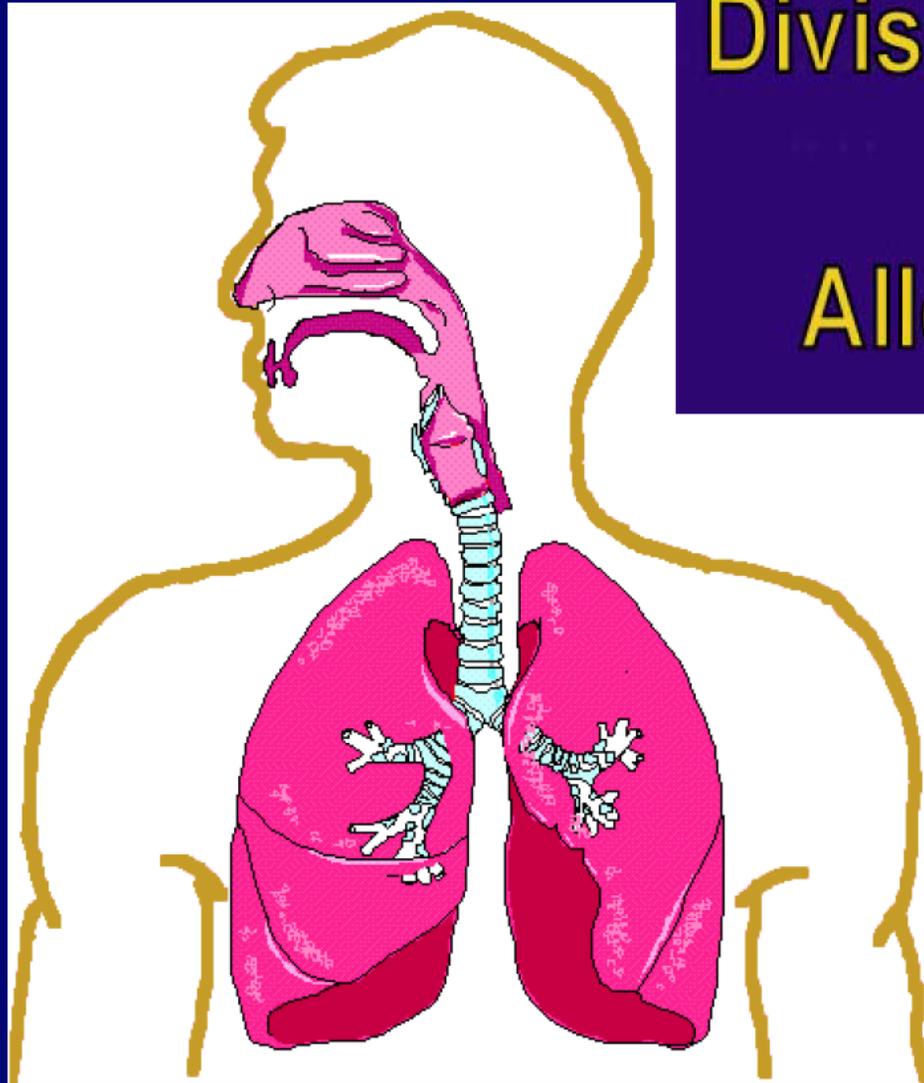
Drug Product-DMFs

10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		
11	Have draft container labels been provided?	X		
12	Has the draft package insert been provided?	X		
13	Has an investigational formulations section been provided?	X		
14	Is there a Methods Validation package?	X		
15	Is a separate microbiological section included?	X		

Filable...from CMC



Division of Pulmonary and Allergy Products



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Silver Spring, MD 20993-0002

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FAX: 301-796-9728



Food and Drug Administration
Division of Pulmonary and Allergy Products



Spiriva Respimat Filing Meeting

1/29/2008

28

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/s/

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Ali Al-Hakim
1/29/2008 01:09:20 PM
CHEMIST



NDA 21-936

NDA ACKNOWLEDGMENT

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

Attention: Jeffrey R. Synder
Executive Director, Drug Regulatory Affairs

Dear Mr. Synder:

We have received your new drug application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: SPIRIVA® RESPIMAT Inhalation Spray

Date of Application: November 16, 2007

Date of Receipt: November 16, 2007

Our Reference Number: NDA 21-936

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 January 15, 2008 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/oc/datacouncil/spl.html>. 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 be in the Prescribing Information (physician labeling rule) format.

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 and Allergy 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/cder/ddms/binders.htm>.

If you have any questions, call Miranda Raggio, Regulatory Project Manager, at (301) 796-2109.

Sincerely,

{See appended electronic signature page}

Sandy Barnes
Chief, Project Management Staff
Division of Pulmonary and Allergy 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/

Miranda Raggio
11/28/2007 12:02:53 PM
Signing for Sandy Barnes

MEMORANDUM OF MEETING MINUTES

MEETING DATE: April 20, 2005
TIME: 10:30 AM
LOCATION: Parklawn Conference Room C
APPLICATION: IND 65,127 Spiriva Respimat

FDA Representatives:

Badrul A. Chowdhury, M.D., Ph.D., Division Director
Shinja Kim, Ph.D., Pharmacology and Biopharmaceutics Reviewer
Emmanuel Fadiran, Ph.D., Clinical Pharmacology and Biopharmaceutics Team Leader
Lisa Kammerman, Ph.D., Biostatistics Reviewer
Richard Lostritto, Ph.D., CMC Team Leader
Eugenia Nashed, Ph.D., CMC Reviewer
Sally Seymour, M.D., Medical Officer
Eugene Sullivan M.D., Deputy Division Director
Sue Jane Wang, Ph.D., Acting Biostatistics Team Leader
Anthony M. Zeccola, Regulatory Management Officer

Boehringer Ingelheim Representatives:

Burkhard Blank, M.D., Sr. VP - Medical and Drug Regulatory Affairs
Herrad Krenkel, Ph.D., Head - Corporate Drug Regulatory Affairs
Marty Kaplan, M.D., J.D., VP - Drug Regulatory Affairs
Bernd Disse, M.D., Therapeutic Area Head
Eben Rubin, M.D., Director - Medical
Demetri Pavia, Ph.D., Team Member Medicine
Sabine Kattenbeck, Ph.D., International Project Leader
Stefan Leiner, Ph.D., Pharmaceutical Expert
Gerd Jilge, Ph.D., Technical Drug Regulatory Affairs
Helen Dewberry, B.Sc. (Honors), Project Biostatistician
Theresa Maloney, R.Ph., Senior Associate Director Drug Regulatory Affairs
Jeff Snyder, Director Drug Regulatory Affairs

Pfizer Representatives:

Birning Wong, Drug Regulatory Affairs
Tom D'Eletto, M.D., Medical

Background

Boehringer Ingelheim (BI) submitted a Type B meeting request dated December 9, 2004, to discuss Pre-NDA Planning. BI also submitted a briefing package dated March 16, 2005, which contained a list of questions to be discussed at this meeting. Upon review of the briefing package, the division responded to BI's questions via fax on April 14, 2005. The content of that fax is printed below. Any discussion that took place at the meeting is captured directly under the relevant original response including any changes in our original position. BI's questions are in **bold italics**; FDA's response is in *italics*; meeting discussion is in normal font.

Discussion

- 1.1 In several sections of the proposed labeling, information from the approved SPIRIVA HandiHaler labeling that is applicable to SPIRIVA Respimat is provided verbatim. The annotated package insert for SPIRIVA RESPIMAT will list the SPIRIVA HandiHaler package insert as the reference for this type of information. Does the Division concur with this approach?***

The Division agrees that some information from the Spiriva HandiHaler package insert will be applicable to the Spiriva Respimat package insert. The specific language will be a review issue.

- 1.2 Does the Division agree with the proposed concept for presentation of the safety data for the Adverse Reactions Section of the SPIRIVA RESPIMAT proposed Package Insert?***

We agree that the proposed adverse event table is reasonable for NDA submission. The format and content of the table to be included in the product labeling will be a review issue.

- 1.3 For the Clinical Studies section of the proposed Package Insert, three figures are included to show representative data from the 1-year, 12-week and 4-week Phase III trials. Does the Division have any comments on this approach?***

The figures in the Clinical Studies section of the proposed Package Insert will be a review issue.

- 1.4 Does the Division have any general or preliminary comments on the draft labeling components included in the pre-NDA meeting package?***

No.

- 2.1 Based on the draft Table of Contents provided for Module 5, does the Division agree with the general organization and content of the clinical data section and cross-referencing strategy for the NDA?***

Yes.

2.2a Does the Division agree with the proposed organization of the Clinical Summary of Efficacy (2.7.3)?

Yes.

2.2b Integration of the efficacy datasets will include the overall integration of efficacy results in all studies with efficacy endpoints and the integration of studies with common trial design/duration. Does the Division agree with the proposed approach to the integration of efficacy results?

Yes.

You indicated there were too few non-white patients to do a subgroup analysis for race. Although the number of non-white subjects may be low, submit a subgroup analysis for race for the combined one-year trials.

The small number of non-white subjects in the database will be an important review issue.

2.3a Following the FDA feedback on the acceptability of the Mahler's TDI, we are no longer seeking a label claim for dyspnea. The analysis plans for the two one-year trials were predicated on establishing the dyspnea claim. As this is no longer the case, BI would like to change the order of assessment for international registration. The proposed order of assessment is 1. Trough FEV1 response, 2. SGRQ (total score), 3. Mahler TDI (focal score) and, 4. COPD exacerbations. The trials will be analyzed separately for trough FEV1 response and SGRQ and combined for Mahler TDI and COPD exacerbations. A multiple testing procedure will be used to control the family-wise type I error rate. Is this reordering of the endpoints acceptable?

If the data have not been analyzed and the studies remain blinded, the reordering is acceptable for FDA review. The NDA will need to include a timeline describing the status of the trials, the date of the database locks, the unblinding of the database and any other pertinent information to ensure us the reordering of the endpoints and the changes to the statistical methods section were not affected by a review of the trial data.

Because you do not intend to use the Mahler TDI to pursue a claim for dyspnea, we question the need for assessing the Mahler TDI. If the proposed serial testing approach fails to reject the null hypothesis for the TDI, then COPD exacerbations cannot be assessed.

BI indicated that the data have not been analyzed and the ongoing studies remain blinded. Unlocking of the database is scheduled for July, 2005. BI indicated that

the rationale for maintaining the Mahler TDI as one of the four important endpoints was to support their application in Europe, which requires a symptom assessment.

The data from the two one-year studies will be pooled to assess the Mahler TDI and COPD exacerbation endpoints. BI will assess the Mahler TDI ahead of COPD exacerbations in the analysis because the pooled studies power for the assessment of the Mahler TDI is greater than the power for the assessment of COPD exacerbations

2.3b *In the current one-year trial protocol the method for controlling the family-wise type I error rate (the probability to reject at least one true null hypothesis, regardless which subset of null hypotheses happens to be true) is serial testing of 10 mcg (vs. placebo) and then 5 mcg (vs. placebo) for each endpoint. Each significance test is performed at the 5% level (2-sided). The efficacy for each dose for each endpoint can only be tested if all the previous tests were significant. Instead of serial testing of 10 mcg followed by 5 mcg, BI would now like to propose parallel testing of 5 mcg and 10 mcg using Fisher's protected least significant difference (LSD). (For COPD exacerbations the Kruskal-Wallis test followed if significant by the Wilcoxon-Mann-Whitney test will be used as a non-parametric equivalent of Fisher's protected LSD.) For each endpoint the type I error will be controlled by testing the null hypothesis of no location difference amongst the three treatments. If this null-hypotheses is rejected, pair-wise comparisons will be used to test each dose against placebo. In order to proceed to testing the next endpoint the F-test and at least one of the pair-wise comparisons must be significant (in favour of Spiriva) for each previous endpoint. BI is seeking to register one dose only. Does the FDA agree that this combination of serial testing of endpoints and parallel testing of doses using Fisher's protected LSD adequately controls the family-wise type I error at 5%?*

- a. Please explain why the original approach of testing the 10 mcg dose versus placebo followed by testing the 5 mcg dose versus placebo is "no longer optimal" (page 116) and, therefore, why you are proposing a new approach for controlling the overall Type I error rate.*
- b. Describe how you plan to select one dose for approval and marketing and how this plan affects your statistical approach.*
- c. Although the proposed approach appears to control the family-wise type I error at 5%, the approach carries risks that could affect the approvability of the NDA:*

A goal of your NDA submission is to gain approval for either the 5 mcg or 10 mcg dose based on the results for trough FEV1. The null hypotheses of no difference among the three treatment groups, as stated in your proposal, is not of primary interest in a regulatory setting.

If the null hypothesis of no difference among the three treatment groups is not rejected, then further statistical testing is not permitted. Even if one of the

pairwise comparisons between one of the doses and placebo is statistically significant at a nominal level of 0.05, we would conclude the study did not achieve its objective of demonstrating the efficacy of Spiriva.

Although page 118 indicates the proposed two-step procedure is Fisher's LSD method, this method is not being fully implemented. Fisher's LSD calls for the testing of all pairwise comparisons when the global hypothesis is statistically significant. As described on page 177 and elsewhere, however, you will be testing only two of the three possible pairwise comparisons. Because of this restriction, I'm conjecturing the family-wise error rate could be less than .05.

- d. Your proposal may lead to undesired but statistically valid outcomes. For example, the results from one of the studies may show 5 mcg is statistically significant for FEV1 and 10 mcg is not, while the 10 mcg is statistically significant for SGRQ.*
- e. What is of interest are the comparisons of each dose with placebo. The following two null hypotheses are consistent with the goal of gaining approval of one of the doses:*
 - i. No difference between 5 mcg and placebo.*
 - ii. No difference between 10 mcg and placebo.*

For testing pairwise comparisons and for controlling the Type I error, we recommend that you use an approach that does not require a test of the global hypothesis of no difference among the three treatment groups. A Dunnett's test is one possible method. By doing so, you may avoid the potential pitfall where the global test is non-significant and one of the pairwise comparisons is nominally significant.

The Division clarified that the above comment should state, “we recommend you consider using an approach that does not require a test of the global hypothesis.” BI acknowledged that with the current proposal, there was potential for the global test to be not significant even though one of the pairwise comparisons (doses) would have been significant. BI explained that the proposal was based upon its analysis of the data generated from the studies that have been completed thus far in the development program.

Moreover, single-step procedures permit the estimation of confidence intervals which are not possible with step-down procedures. Interpretation of results from step-down procedures must rely on p-values.

The majority of the meeting time focused on the responses provided to BI by the Biostatistics Review Team in questions 2.3a and 2.3b (above) and “Additional Comments” (below). The discussion focused around the complexity of the

analysis of the four important endpoints and the two potential doses. The Division provided feedback, but a consensus was not reached on the most appropriate analysis plan. However, an agreement was reached for BI to consider the comments provided and submit a detailed statistical analysis plan to the Division for feedback. NOTE: See **Addendum to Meeting Minutes** below.

BI raised an additional issue towards the end of the meeting, which was not in the briefing package. BI is using the Mahler TDI to support its application for the EU, but the Mahler TDI cannot be used to support a dyspnea claim in the United States. BI would like to have the analysis order for the United States be the trough FEV1, SGRQ, and COPD exacerbations and the analysis order for the EU to be the trough FEV1, SGRQ, Mahler TDI, and COPD exacerbations. However, BI is working under a common protocol for its multinational studies. BI inquired if there was a way for the analysis for the United States to not require a win on the Mahler TDI to proceed to the COPD exacerbations endpoint. Dr. Chowdhury indicated that this issue would require some internal discussion and suggested that BI incorporate a proposal in the submission of the statistical analysis plan. The Division will review BI's proposal and respond accordingly.

2.4 *If the dose to be proposed for marketing achieves a statistically significant difference and demonstrates an improvement by at least 4 units (in comparison to placebo) in SGRQ total score, in both studies, will the Agency allow BI to include a label statement regarding improvement in quality of life attributable to SPIRIVA RESPIMAT in the Clinical Studies section of the US PI?*

If you show a statistically and clinically significant effect on the SGRQ total score in both one-year studies, we will consider describing the results in the product label. The specific language will be a review issue. The application should contain adequate validation of the instrument, including the minimal clinically important effect size.

2.5 *BI plans to use MedDRA and the BI collapse terms to report the AEs in the pertinent NDA documents and the proposed package insert. Is this approach acceptable?*

- *Clarify that the procedure for collapsing the MedDRA terms has been standardized prior to unblinding the data*
- *Submit the procedure for collapsing the terms with the NDA*
- *Submit all AE listings using the original MedDRA preferred terms and using the BI collapsed terms*

2.6 *We plan to describe integrated safety information in the Summary of Clinical Safety. A stand-alone ISS is not anticipated. Does the FDA have any comments on this proposal?*

Your Summary of Clinical Safety should include a summary of the postmarketing adverse events for Spiriva HandiHaler and a summary of a literature review of safety information related to tiotropium bromide.

Also for the common adverse events (Section 2.1), explore for a potential dose relationship and explore for a time to onset relationship.

Submit summary results of all completed postmarketing studies of tiotropium. These summaries should specifically address cardiac safety findings from these studies.

- 2.7** *Within the Summary of Clinical Safety, BI will include subgroup analyses for gender, age, COPD severity, oral steroid use, inhaled steroid use and smokers/ex-smokers; however this subgroup analysis will only be done for the combined data from the two 1-year trials 205.254 and 205.255. Is this acceptable?*

Subgroup analysis for the combined 1-year trials is acceptable. However, we request you also pool the data from all six studies (205.249, 204.250, 205.251, 205.252, 205.254, and 205.255) for the tiotropium bromide inhalation spray and placebo groups to perform subgroup analyses.

In addition, the pooled data from all six studies should be analyzed for less common adverse events.

- 2.8** *There are 15 patients who completed the 4-week or the 12-week trials and were enrolled into one of the two 1-year Phase III trials. Section 1.2.1 of the Summary of Clinical Safety describes how we plan to report safety data for these patients. Is this approach acceptable to the Division?*

Your approach to list the patient under the trial with the longest duration is acceptable to summarize the overall extent of exposure. However, adverse events for the 15 patients should be reported in the trial in which the adverse event occurred.

- 3.1** *For the Spiriva Respimat NDA, Module 4 will only contain one study report (U01-1720) with a cross-reference to the Spiriva HandiHaler NDA for the entire nonclinical section (Module 4). Additionally, BI does not plan to include a non-clinical summary document (CTD 2.6) in the Spiriva Respimat NDA. Is this acceptable to the Division?*

Yes, it is acceptable.

- 3.2** *Other than modifications to the dose multiples due to the different population, the non-clinical portions of the package insert remain identical to the Spiriva HandiHaler NDA (reference NDA 21-395, 07 April 2003 fax from FDA). BI*

plans to provide justifications and support for the dose multiples in the Spiriva Respimat package insert in the nonclinical overview document. Is this acceptable to the Division?

Yes, it is acceptable.

4.1 *Does FDA agree with our proposal on the level of information to be presented in the NDA for the drug substance versus the information incorporated from the DMF?*

Yes. For the drug substance, include the maximum storage interval (retest time), and Microbiological purity testing results in the specifications. Provide stability data to support revised specifications.

4.2 *Does the FDA agree with our proposal to submit a detailed description of the manufacturing process in lieu of an actual Master Batch Record?*

You may provide a suitably detailed description with an adequate amount of data to allow a thorough CMC and Microbiology review. However, this is a high risk approach; if the description and data are inadequate, approvability may be threatened. As stated during the Combivent Respimat p-NDA meeting, we suggest that in addition to the description of the manufacturing process, also provide a certified translation of the Master Batch Record (MBR) to best facilitate the review.

Verify that the sterile process validation will cover all manufacturing and container closure changes, i.e., before manufacture of the NDA and stability batches.

Dr. Nashed indicated that since there have been a large number of changes, the Division wants to see all changes addressed in the validation studies.

4.3 *Does FDA agree that for Spiriva Respimat a second ethylene oxide contract sterilizer for the primary packaging material can be included in an Annual Report?*

No. Submit any proposed post-approval changes which may affect sterility as a supplemental application. Provide supporting validation studies, including degassing and residuals testing.

Confirm that only one sterilization process (Class 100 versus ETO) will be used for the initial commercial manufacture.

Drs. Nashed and Lostritto reiterated that while it is acceptable to have 2 different processes during development, it would be a better approach to file the NDA with the preferred method. Then if BI decides that both methods are necessary, submit the second method for review as an sNDA.

4.4 Boehringer Ingelheim would appreciate the Agency's current thinking on comparability protocols as to what basic elements and specific issues should be considered in developing a comparability protocol for changes in primary plastic components.

Clarify the specific changes for which specified components you are proposing and when you are planning to submit the protocol. We recommend a narrow focus and well defined changes for a very limited number of suppliers. Specify in the protocol what supportive data will be submitted and when it will be provided.

We recommend prior discussion with Agency regarding:

Exact components subject (and not subject) to the protocol

Individual vendor qualification program for identical materials (this applies to exact resin AND additives)

Provide for rigorous, well designed, and complete data-based comparisons for any changes in the additive package (e.g., antioxidants, UV inhibitors, release agents, colorant, etc.) for formulation and/or mouth contact components

Exclude changes in material type from the protocol for any portion of the device/container closure.

Dr. Lostritto reminded BI of the new Good Review Management Practice (GRMP) Guidance Document (see GRMP reference in "Additional Comments" below), which implements new internal review timelines for FDA Review Divisions. In order for reviewers to be able to complete reviews within the specified timelines, applications must be "complete" at the time of submission (including stability data). Product labeling will reflect the data that is submitted at the time of initial NDA submission.

4.5 Is FDA in agreement with Boehringer Ingelheim's stability program to stop testing on the 2nd set (3 batches of cartridges containing alternate (b) (4) amend the NDA approx. 4 months after submission with additional stability data allow the 3rd set of the primary stability (final commercial process) to satisfy the requirements for accelerated and long term stability testing of the first three production batches of drug product?

Yes, however the duration of the expiry period is a review issue and will be based on the primary stability data from the batches manufactured according to the final process and with the final container closure. Other stability data may be considered supportive stability data to the degree that it matches the to-be-marketed case. Expiry will be determined by the quality and quantity of the primary and supportive stability data. Clarify when the 3rd set of stability data is expected to be provided

Explain your proposal for “reduced testing” for the 2nd set of stability data (p. 271). Are all attributes and methods the same as for the 1st and 3rd sets?

- 4.6 Does the FDA agree with the proposal to submit 2 executed batch records, one from the 1st set of stability batches that support product used in clinic and one from the 3rd set of stability batches representing the maximum production scale batch size (b) (4)?**

Yes. Provide available COAs (or batch analysis reports) for NDA and stability batches representing different strengths, manufacturing scales and changes in the sterilization process or packaging materials, for comparison.

- 4.7 Does FDA agree on our proposal to submit with a methods validation package only for the drug product analytical procedures?**

Yes, provided that the validated methods for drug substance are submitted to the updated DMF(s) and those will have an adequate status upon review. Also, submit a statement about changes in methods and specifications for the drug substance since the approval of NDA 21-395.

- 5.1 Does FDA concur that submission of the product labeling in SPL format will not be required for this NDA, targeted for submission in late 2005/early 2006?**

Yes.

- 5.2 Study data (SAS xpt files in the crt folder) will be provided for ten SPIRIVA RESPIMAT clinical trials and one SPIRIVA HandiHaler trial. Does the Division agree with this proposal?**

Yes.

- 5.3 The data tabulation datasets will be prepared according to the CDISC Submission Data Standards Version 2.0. By taking this approach, these datasets will be similar in structure and format to those provided in the SPIRIVA HandiHaler NDA 21-395. Is this approach acceptable?**

Yes.

- 5.4 ECGs for a subset of the patients in the 1-year Phase III Trials 205.254 and 205.255 are being recorded digitally. The crt folder will contain an ECG subfolder for these two trials where centralized ECGs were performed and will contain the annotated ECG waveform datasets as specified in HL7 standards. Is this acceptable to the Division?**

Yes.

Attachment 1 Question: BI submitted plans to evaluate the “reduction in COPD exacerbations” endpoint in both SPIRIVA RESPIMAT and SPIRIVA HandiHaler clinical trials to establish wording in the label describing tiotropium effects in reducing COPD exacerbations in patients. Does the FDA agree with the proposed concept? If not, is there specific guidance that we should consider in evaluating the tiotropium effects on reducing COPD exacerbations?

If you show a statistically and clinically significant reduction in COPD exacerbations in the combined one-year trials (205.254 and 205.255) and substantiate the finding in a second clinical trial, we would consider describing the finding in the product label. Whether 205.266 provides adequate data to substantiate the finding will be a review issue. In addition, the exact wording in the product label will be a review issue.

Additional Comments:

CMC

Provide comprehensive information (table format preferred) linking the clinical batches to CMC changes implemented during drug product development, e.g., strength, batch scale, change in sterilization procedure, change in polypropylene, different Respimat models, etc.

Since the NDA will be submitted in the electronic and paper format, provide comprehensive summaries and overviews with consecutive page numbers and cross-references.

- ◆ *To other CMC parts/data in submission*
- ◆ *To other Disciplines’ data and information*
- ◆ *Lack of this information may impact fileability*

Verify that you will adhere to all agreements from the EOP2, p-NDA meetings and other meetings for the Respimat products that pertain to this NDA; bring any specific deviations(s) to our attention. The proposed specifications and expiry period will be evaluated during NDA review.

Non-clinical

Address the safety qualification of degradants, impurities, leachables and extractables, if applicable, in the NDA submission.

Biostatistics

- *If a study’s randomization was stratified, the analyses need to include treatment-by-covariate interactions representing the stratification.*

For the SGRQ endpoint:

- *Include analyses of each domain in addition to the analyses of the total score.*
- *Provide a rationale for the potential use of this endpoint in labeling. If you believe the SGRQ adds information important for the patient and prescriber, then the results may need to be reported regardless of statistical significance.*

The Division clarified this point. As stated in the response to question 2.4, the Division will consider describing the results of the SGRQ in the product label. The specific language will be a review issue.

COPD exacerbations:

- *When analyzing the combined data from 205.254/205.255, include terms for clinical study and other variables used to stratify the randomization.*
- *The proposed comparison of number of exacerbations per patient year may be problematic if not all subjects are followed for 48 weeks. In the absence of complete follow-up, the change in risk over time may impact the estimate of the treatment effects.*
- *Analyses using length of exposure or other post-randomization variables will be considered exploratory.*
- *For those subjects experiencing at least one exacerbation, provide analyses of the severity of the exacerbation and all subsequent exacerbations at the patient-level. For example, include analyses of the number of subjects experiencing one exacerbation, two exacerbations, three exacerbations and so on. Additionally, classify exacerbations by severity.*
- *If the VA study cannot be used as a confirmatory study, we will consider the pooled study as only one AWCS. In this case, a p-value less than .001 will be required to conclude efficacy of Spiriva Respimat based on the results from the pooled study.*

The Division retracted this last bullet point during the pre-NDA meeting.

Addendum to Meeting Minutes

As discussed during the meeting (see **discussion under 2.3 above**), BI submitted a detailed analysis plan on April 29, 2005 as submission number 109 to the IND, the following comments reflect the Divisions review of that submission:

The proposal for the sequential testing of endpoints is acceptable.

The proposal to proceed to the exacerbations endpoint for the US NDA, regardless of the significance of the TDI endpoint, is acceptable. However, the Division expects the NDA submission to include the data and analyses for the TDI endpoint for our review.

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this page is the manifestation of the electronic signature.**

/s/

Anthony Zeccola
5/18/05 11:47:12 AM