

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207070Orig1s000

OTHER REVIEW(S)

LABEL AND LABELING REVIEW

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

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

Date of This Review:	September 10, 2015
Requesting Office or Division:	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Application Type and Number:	NDA 207070
Product Name and Strength:	Spiriva Respimat (Tiotropium Bromide) Inhalation Spray 1.25 mcg per actuation
Product Type:	Single-Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Boehringer Ingelheim
Submission Date:	May 8, 2015
OSE RCM #:	2015-2040
DMEPA Primary Reviewer:	Lissa C. Owens, PharmD
DMEPA Team Leader:	Kendra Worthy, PharmD

1 REASON FOR REVIEW

DPARP requested that we review the proposed container labels and carton labeling for areas that may lead to medication errors. Spiriva Respimat labels were found acceptable under NDA 207070¹, however, [REDACTED] (b) (4) the new indication for the long-term, once-daily, maintenance treatment of asthma in patients 12 years of age and older. All other product characteristics remain the same.

2 MATERIALS REVIEWED

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

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B-N/A
Human Factors Study	C-N/A
ISMP Newsletters	D-N/A
FDA Adverse Event Reporting System (FAERS)*	E-N/A
Other	F-N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Spiriva Respimat is currently marketed as 2.5 mcg strength for the long-term, once-daily maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), and for reducing COPD exacerbations. We originally reviewed the labels and labeling under this application for a new asthma indication [REDACTED] (b) (4)

[REDACTED]

[REDACTED]

¹ Owens, Lissa C. Proprietary Name Review for Spiriva Respimat (NDA 207070). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 February. 6 OSE RCM No.: 2015-1959.

We performed a risk assessment of the proposed container labels and carton labeling, to identify deficiencies that may lead to medication errors.

DMEPA finds the proposed container labels and carton labeling acceptable.

4 CONCLUSION

DMEPA concludes that the proposed container labels and carton labeling are acceptable.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Spiriva Respimat that Boehringer Ingelheim submitted on September 2, 2015.

Table 2. Relevant Product Information for Spiriva Respimat	
Initial Approval Date	September 24, 2014
Active Ingredient	Tiotropium Bromide
Indication	<ul style="list-style-type: none"> The long-term, once-daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), and for reducing COPD exacerbations <p>Proposed 1.25 mcg strength:</p> <ul style="list-style-type: none"> The long-term, once-daily, maintenance treatment of asthma in patients 12 years of age and older
Route of Administration	Oral Inhalation
Dosage Form	Inhalation Spray
Strength	2.5 mcg (approved) and 1.25 mcg (proposed)
Dose and Frequency	<ul style="list-style-type: none"> Treatment of COPD: 2 inhalations of SPIRIVA RESPIMAT 2.5 mcg once-daily <p>Proposed:</p> <ul style="list-style-type: none"> Treatment of asthma patients 12 years and older: 2 inhalations of SPIRIVA RESPIMAT 1.25 mcg once-daily
How Supplied	Carton containing one SPIRIVA RESPIMAT cartridge and one SPIRIVA RESPIMAT inhaler
Storage	Store (b) (4) at 77°F (25°C); excursions permitted to 59°F to 86°F (15°C to 30°C)

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

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/s/

LISSA C OWENS
09/10/2015

KENDRA C WORTHY
09/10/2015

PMR/PMC Development Template

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

NDA/BLA # 207-070
Product Name: Spiriva Respimat (tiotropium)

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

PMR/PMC Schedule Milestones:	Final Protocol Submission:	NA
	Study/Trial Completion:	05/2015
	Final Report Submission:	10/2016
	Other:	NA

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

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

Currently Spiriva Respimat (tiotropium) is not indicated in pediatric patients less than 12 years of age. Because the drug was ready for approval in adults and adolescents before the pediatric studies were complete, PREA required studies were deferred at the time of approval.

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

Spiriva Respimat (tiotropium) is not available to pediatric asthma patients less than 12 years of age due to lack of efficacy and safety information in this age group. The goal of this study is to determine appropriate dosing and to obtain safety data in patients 6 to 11 years of age.

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

If not a PMR, skip to 4.

– **Which regulation?**

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

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

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

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

- Analysis of spontaneous postmarketing adverse events?

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

- Analysis using pharmacovigilance system?

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

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

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

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

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

The trial is a randomized, double-blind, placebo-controlled, parallel arm study in pediatric patients 6 to 11 years of age with asthma.

Required

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

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

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

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

- Does the study/clinical trial meet criteria for PMRs or PMCs?
 - Are the objectives clear from the description of the PMR/PMC?
 - Has the applicant adequately justified the choice of schedule milestone dates?
 - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

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

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

PMR/PMC Development Coordinator:

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

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/s/

SALLY M SEYMOUR
09/01/2015

PMR/PMC Development Template

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PMR/PMC Description: Conduct a 48-week, randomized, double-blind, parallel-group, placebo-controlled, efficacy and safety study of tiotropium delivered via the Respimat device in children 6 to 11 years of age with asthma. The study should evaluate at least two doses of tiotropium and include approximately 125 patients per treatment arm.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	NA
	Study/Trial Completion:	01/2016
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Continuation of Question 4

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Agreed upon:

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/s/

SALLY M SEYMOUR
09/01/2015

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

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

Memorandum

Date: August 20, 2015

To: Jessica Lee, Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
(DPARP)

From: Roberta Szydlo, Senior Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Kathleen Klemm, Team Leader, OPDP

Subject: NDA 207070
OPDP labeling comments for Spiriva[®] Respimat[®] (tiotropium bromide) inhalation spray, for oral inhalation (Spiriva Respimat)

In response to DPARP's consult request dated October 9, 2014, OPDP has reviewed the draft labeling (Package Insert [PI], Instructions for Use [IFU], and Carton/Container Labeling) for Spiriva Respimat.

PI and IFU:

OPDP's comments on the PI and IFU are provided directly below and are based on the draft labeling titled "207070 uspi 080715 clean.docx" (attached) that was provided via email from DPARP on August 7, 2015.

Carton/Container Labeling:

OPDP has reviewed the proposed carton and container labeling for the 1.25 mcg strength submitted by the applicant on May 8, 2015, (eCTD sequence # 0016) and located at the following:

- <\\cdsesub1\evsprod\nda207070\0016\m1\us\ct6594a.pdf>
- <\\cdsesub1\evsprod\nda207070\0016\m1\us\l6595a.pdf>
- <\\cdsesub1\evsprod\nda207070\0016\m1\us\l6596a.pdf>
- <\\cdsesub1\evsprod\nda207070\0016\m1\us\l6598a.pdf>

- <\\cdsesub1\evsprod\nda207070\0016\m1\us\ct6600a.pdf>
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We have no comments at this time on the proposed carton and container labeling.

Thank you for your consult. If you have any questions, please contact Roberta Szydlo at (301) 796-5389 or roberta.szydlo@fda.hhs.gov.

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/s/

ROBERTA T SZYDLO
08/20/2015

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

PATIENT LABELING REVIEW

Date: June 25, 2015

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

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

From: Sharon W. Williams, MSN, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: DMPP Concurrence with Submitted: Instructions for Use
(IFU)

Drug Name (established name): SPIRIVA RESPIMAT (tiotropium bromide)

Dosage Form and Route: Inhalation Spray
Application

Type/Number: NDA 20-7070

Applicant: Boehringer Ingelheim Pharmaceuticals, Inc.

1 INTRODUCTION

On August 15, 2014, Boehringer Ingelheim Pharmaceuticals, Inc. submitted for the Agency's review an Original New Drug Application. The application proposes a new indication for the long-term, once daily, add-on maintenance treatment of asthma in patients 12 years of age and older who remain symptomatic on a least inhaled corticosteroids for SPIRIVA RESPIMAT (tiotropium bromide) Inhalation Spray. SPIRIVA RESPIMAT (tiotropium bromide) Inhalation Spray is currently indicated for the long-term, once-daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), and for reducing COPD exacerbations. On October 9, 2014, the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Instructions for Use (IFU) for SPIRIVA RESPIMAT (tiotropium bromide) Inhalation Spray.

This memorandum documents the DMPP review and concurrence with the Applicant's proposed Instructions for Use (IFU) for SPIRIVA RESPIMAT (tiotropium bromide) Inhalation Spray.

2 MATERIAL REVIEWED

- Draft SPIRIVA RESPIMAT (tiotropium bromide) Inhalation Spray IFU received on August 15, 2014, and received by DMPP on June 24, 2015.
- Draft SPIRIVA RESPIMAT (tiotropium bromide) Inhalation Spray Prescribing Information (PI) received on August 15, 2014, revised by the Review Division throughout the review cycle, and received by DMPP on June 24, 2015.
- SPIRIVA RESPIMAT (tiotropium bromide) Inhalation Spray IFU approved September 24, 2014.

3 CONCLUSIONS

We find the Applicant's proposed IFU is acceptable as submitted.

4 RECOMMENDATIONS

- Consult DMPP regarding any additional revisions made to the Prescribing Information (PI) to determine if corresponding revisions need to be made to the IFU.

Please let us know if you have any questions.

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/s/

SHARON W WILLIAMS
06/25/2015

MELISSA I HULETT
06/25/2015

CLINICAL INSPECTION SUMMARY

DATE: March 31, 2015

TO: Jessica Lee, Pharm.D., Regulatory Project Manager
Stacy Chin, M.D., Medical Officer
Anthony Durmowicz, M.D., Cross Discipline Team Leader
Division of Pulmonary, Allergy and Rheumatology Products (DPARP)

FROM: Anthony Orenca, M.D., F.A.C.P.
Medical Officer, GCP Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H.
Team Leader, GCP Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

Susan D. Thompson, M.D. for
Kassa Ayalew, M.D., M.P.H.
Branch Chief, GCP Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 207070

APPLICANT: Boehringer-Ingelheim Pharmaceuticals, Inc.

DRUG: tiotropium Respimat[®] inhaler device (Spiriva[®] Respimat[®])

NME: No

THERAPEUTIC CLASSIFICATION/REVIEW: standard therapy

INDICATION: Treatment of patients with asthma

CONSULTATION REQUEST DATE: October 15, 2014

INSPECTION SUMMARY GOAL DATE (original): March 31, 2015

DIVISION ACTION GOAL DATE June 15, 2015

PDUFA DATE: June 15, 2015

I. BACKGROUND:

Tiotropium is a long-acting orally inhaled anticholinergic bronchodilator approved for the maintenance treatment of chronic obstructive pulmonary disease (COPD). The sponsor has submitted the combination product NDA, oral tiotropium inhalation solution delivered via the Respimat® inhaler device, for an asthma indication.

Two foreign clinical sites were selected for inspection of three multinational adequate and well-controlled clinical trials (205.416, 205.419, and 205.444) submitted in support of the applicant's NDA. These foreign clinical sites were selected for audit, since domestic data were insufficient for the adult and adolescent study populations. A single domestic clinical site was inspected for a fourth study (205.418). These sites participated in a safety and efficacy clinical trial, and had a large number of enrolled subjects or large treatment effects.

Study 205.416

Study 205.416 was a Phase 3 multicenter, randomized, double-blind, placebo-controlled parallel-group study comparing tiotropium 5 µg daily versus placebo in addition to usual care over 48 weeks. The study evaluated the long term efficacy and safety of tiotropium inhalation solution delivered by the Respimat® inhaler compared to placebo added to usual care in patients with severe persistent asthma over a 48-week study period.

Outpatient study subjects, aged 18 to 75 years, with FEV1 ≤ 80% predicted and FEV1 ≤ 70% of FVC, and who had had one or more asthma exacerbations in the past year were eligible. The efficacy co-primary endpoints were: (1) peak FEV1 response (within 3 hours post dosing), (2) trough FEV1 response after 24-weeks of treatment (based on the individual trial) and (3) time to first severe asthma exacerbation during 48-week treatment (based upon pooled data from trials Study 205.416 and Study 205.417).

Study 205.419

Study 205.419 was a Phase 3 multicenter, randomized, double-blind, double-dummy, active- and placebo-controlled, parallel-group study comparing two doses of tiotropium (2.5 and 5 µg) to placebo or salmeterol over 24 weeks on top of maintenance therapy with an inhaled corticosteroid controller medication. The primary objective was to evaluate the

long term efficacy and safety of tiotropium inhalation solution (2.5 and 5 µg once daily, administered in the evening) delivered by the Respimat® inhaler compared to placebo and salmeterol (administered twice daily) in patients with moderate persistent asthma.

Outpatient study subjects, age 18 - 75 years, who were non-smokers or ex-smokers with < 10 pack years and smoking cessation at least one year prior to enrollment, and on maintenance treatment with a medium dose of inhaled corticosteroids were eligible to be randomized into the study. The co-primary study endpoints were peak FEV1 response (within 3 hours post evening dosing) and trough FEV1 response after 24 weeks treatment.

Study 205.444

Study 205.444 was a Phase 3 multicenter, randomized, double blind, placebo-controlled, parallel group study to assess the efficacy and safety over 48 weeks of orally inhaled tiotropium bromide (2.5 µg and 5 µg once daily) delivered by the Respimat® inhaler in adolescents (12 to 17 years old) with moderate persistent asthma. The primary study objective was to assess the long term efficacy (over 48 weeks, but with primary/main secondary endpoint analysis after 24 weeks of treatment) and safety of tiotropium bromide inhalation solution (2.5 or 5 µg) once daily administered with the Respimat® inhaler in the evening, compared to placebo, in adolescent patients (12 to 17 years old) with moderate persistent asthma, on top of maintenance therapy with an inhaled corticosteroid controller medication.

Outpatient study subjects, aged 12 to 17 years with a documented minimum 3 month history of asthma, pre-bronchodilator FEV1 $\geq 60\%$ and $\leq 90\%$ predicted, or an increase in FEV1 $\geq 12\%$ and 200 mL 15-30 minutes after 400 µg salbutamol (albuterol) were eligible to be randomized into study. The primary study endpoint was FEV1 peak 0-3 hour response after 24 weeks of treatment

Study 205.418

Study 205.418 was a randomized, double-blind, double dummy, placebo- and active-controlled, parallel-group study design comparing tiotropium (two doses) with placebo or salmeterol over 24 weeks on top of maintenance therapy with an inhaled corticosteroid controller medication. The primary study objective was to evaluate the long term efficacy and safety of tiotropium inhalation solution (2.5 and 5 µg once daily administered in the evening) delivered by the Respimat® inhaler compared to placebo and salmeterol (administered twice daily) in adult patients with moderate persistent asthma.

The co-primary endpoints were peak FEV1 response (within 3 hours post evening dosing) and trough FEV1 response after 24 weeks treatment.

II. RESULTS:

Name of CI Location	Study Site/Protocol/Number of Subjects Enrolled (n)	Inspection Date	Classification*
Olaf Schmidt, M.D. KPPK GmbH, Lungen-und Bronchialkunde Emil-Schuller-Str. 29 56068 Koblenz, Germany	Site #49005 Protocol 205.416 Subjects=40 Site #49057 Protocol 205.419 Subjects=43	January 12-21, 2015	NAI
Carlos Quilodran, M.D. Hospital Gustavo Fricke-Alvarez #1532 2570017 Viña del Mar Chile	Site #56001 Protocol 205.444 Subjects=38	January 19-22, 2015	Preliminary: VAI
Stephen Tilles, M.D. ASTHMA Inc. 4540 Sand Point Way NE, Suite 100 Seattle, WA 98105	Site #01019 Protocol 205.418 Subjects=22	November 17- December 17, 2014	VAI

*Key to Classifications

NAI = No deviation from regulations. Data acceptable.

VAI-No Response Requested = Deviations(s) from regulations. Data acceptable.

OAI = Significant deviations from regulations. Data unreliable/critical findings may affect data integrity.

Preliminary=The Establishment Inspection Report (EIR) has not been received, findings are based on preliminary communication with the field at the Office of Regulatory Affairs (ORA), or final review of the EIR is pending. Once a final letter is issued by CDER to the inspected entity and the case file is closed, the preliminary designation is converted to a final regulatory classification.

CLINICAL STUDY SITE INVESTIGATOR

1. Olaf Schmidt, M.D, Protocols 205.416/ Site #49005 & 205.419/Site # 49057

Koblenz, Germany

a. What was inspected:

The inspection was conducted in accordance with Compliance Program 7348.811, from January 12 to 21, 2015.

For Study 205.416, a total of 40 subjects were screened, 37 subjects were enrolled, and 35 subjects completed the study. An audit of 37 enrolled subjects' records was conducted. For Study 205.419, a total of 43 subjects were screened, 33 subjects were enrolled, and 32 subjects completed the study. An audit of the 33 enrolled subjects for primary efficacy endpoint and adverse event data was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

b. General observations/commentary:

Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (List of Inspectional Observations) was not issued at the end of the inspection.

During the close out inspection meeting between the FDA and study site investigator, the ORA investigator noted that for Study 205.419, Subject 34, inclusion criteria 9 through 12 were recorded as “no” by study staff on the sponsor worksheet, although “yes” should have been checked indicating the subject met the enrollment criteria. Source data review showed that Subject 34 did in fact meet all inclusion criteria.

c. Assessment of data integrity:

Data submitted by this clinical site appear acceptable in support of this specific indication.

2. Carlos Quilodran, M.D., Protocol 205.444/Site #56001

Viña del Mar, Chile

a. What was inspected:

The inspection was conducted in accordance with Compliance Program 7348.811, from January 19 to 22, 2015. For Protocol 205.444, a total of 38 subjects were screened, 35 subjects were enrolled, and 34 subjects completed the study. An audit of 10 enrolled subjects' records was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

b. General observations/commentary:

Source documents for those enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. However, a Form FDA 483 (Inspectional Observations) was issued at the end of the inspection.

The Form FDA 483 (Inspectional Observations) was provided to DPARP and discussed at length with the DPARP Medical Team. While regulatory deficiencies were observed, the review division determined that these did not have a critical impact in the assessment of the primary study endpoint and overall safety evaluation of this application. Dr. Quilodran responded adequately to the List of Inspectional Observations on February 11, 2015.

Please refer to selected relevant examples below:

- (1) Regarding informed consent and assent documents, the investigation was not conducted in accordance with the investigational plan, and the cases histories were not accurate, adequate, or complete. Specifically,
 - a. Approved versions of the informed consent and assent document forms were not signed by all patients who required re-consenting during the study. For example, Subjects 4441501, 4441502, 4441503 and 4441505 did not sign the assent Version 3.0 July 1, 2011 version approved by the Ethics Committee on August 4, 2011 and their legal representatives did not sign these informed consent document forms.
 - b. Subjects and their representatives were not always consented with the most current version of the assent or informed consent document. For example: Subjects 4441507, 4441508, and 4441509 and their legal representatives signed Version 1.1 approved by the Ethics Committee on December 23, 2010, instead of the current Version 3.0 approved by the Ethics Committee on August 4, 2011. Numerous other subjects were noted to have similar issues.
 - c. Incorrect versions (Version 1.1) of the informed consent and assent documents were signed by Subject 4441523 and legal representative on the January 10, 2012 screening visit. These documents were discarded by the study site and not available for review.

OSI Comment:

In his February 11, 2015 written response to the FDA Form 483, Dr. Quilodran states that for many of the subjects, although more recent documents were approved by the Ethics Committee, the Chilean Ministry of Health had not yet been notified about the updated forms and therefore, subjects could not yet sign those documents.

In these instances, subjects/authorized legal representatives were apprised of new safety information. Additionally, some subjects attended visits without their parents, and therefore, updated consents were not obtained. When contacted, the parents refused to return to the site to complete the forms because the subjects had completed the study. Dr. Quilodran also acknowledged that some subjects had indeed signed outdated informed consent documents and has implemented new procedures to prevent this from happening in the future.

- (2) Protocol-specified order of events for patient visits could not be verified by source data. Specifically:

The electronic diary (AM3 device) which recorded morning and evening PEF and FEV1 values throughout the screening and treatment period were not programmed to correspond with the local time. The electronic diary AM3 questions were required to be answered and PEV and FEV1 readings were required to be taken and verified prior to the study drug administration. Times of the PEV, FEV1 and question responses could not be verified in the data.

The MasterScope® CT PFT which recorded patient pre-PFT values, Respimat® administration, PFT 30 minutes, PFT 60 minutes, PFT two-hour, PFT three-hour values during the treatment period (Visits #2, #4, #6, & #8) was not programmed to correspond with the local time throughout the length of the trial. The values, recorded by the MasterScope® CT PFT, were required to be taken at specified time points related to the AM3 device and inhaled corticosteroid administration documented in the patient charts.

OSI Comment:

OSI discussed these observations with DPARP to assess whether alternative measures were available to account for the PEF and FEV1 device recorded values since the local times were not synchronized. The DPARP Medical Team stated that the electronic diary AM3 device and the MasterScope® CT PFT (a comprehensive pulmonary function testing system on the market for pulmonary function testing [PFT]) calendar date and time tracking data were not relied upon for DPARP's review. Additional evaluations for other time indicators in the NDA submission have been conducted by DPARP in the analyses of the data. DPARP pointed out that the deficiencies in machine-reported time would not have an impact in their efficacy determinations.

In his written response to the Form FDA 483, Dr. Quilodran, stated that after the patient responses into the AM3 electronic diary were “downloaded to the ERT [device]” “and only” after completion of this task was pulmonary function testing (PFT) performed.

(3) Adherence to protocol-specified time frames for pre-dose measurements (pre-PFT), PFT measurements, or study drug recorded administration times were not followed. Specifically,

- a. The 10 minute pre-dose PFT was not always administered within the protocol specified time frame of five to 25 minutes prior to the evening dose of inhaled corticosteroids for all patients. For example, Subject 4441502, on visit date July 22, 2011, pre-dose PFT measurement was administered 41 minutes prior to the evening steroid dose. This was noted for six subjects on eight different occasions.
- b. Recorded administration time for the study drug varied from two seconds to 11 minutes during patient visits. The administration of the study drug is two puffs from the assigned Respimat® inhaler. The end of study drug administration time was used to calculate time intervals of 30 minutes, 60

minutes, 2 hours, and 3 hours for PFTs. For example, the recorded administration time for the study drug for Subject 4441502, on visit date June 22, 2012, was 11 minutes.

- c. PFT at Visits #4, #6, and #8 did not always start within ± 30 minutes maximum difference from the start of the pulmonary function testing at Visit #2. For example, Subject 4441715's pulmonary function testing at the following recorded times: Visit #2 began at 17:07 hours; Visit #4 began at 17:51 hours, and Visit #6 began at 17:46 hours.
- d. Administration of inhaled corticosteroid was documented as being performed prior to the 10 minute pre-dose measurement (pre-PFT) for Subject 4441502 at Visit 8, Subject 4441505 at Visit 8, and Subject 4441508 at Visit 6.

OSI Comment: The DPARP Medical Team considered the above items to be noncritical to measurement of the primary efficacy parameter, FEV1 peak [0-3 (L)] or maximum FEV1 measured within 3 hours following the study drug inhalation.

c. Assessment of data integrity:

Although there were protocol violations described on the Form FDA 483, these cited items do not have a significant impact on the reliability of the study data. Therefore, data submitted by this clinical site appear acceptable in support of this specific indication.

3. Stephen Tilles, M.D., Protocol 205.418/ Site #01019

Seattle, Washington

a. What was inspected:

The inspection was conducted in accordance with Compliance Program 7348.811, from November 17 to December 17, 2014. For Study 205.418, a total of 22 subjects were screened, 10 subjects were enrolled, and 8 subjects completed the study. An audit of 22 enrolled subjects' records was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

b. General observations/commentary:

Source documents for these enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. However, a Form FDA 483 (Inspectional Observations) was issued at the end of the inspection.

The Form FDA 483 (Inspectional Observations) was provided to DPARP and discussed extensively on several occasions with the DPARP Medical Team. Per the DPARP Medical Team, despite the stringent protocol requirements for pre-visit evening and morning doses of study medication and dosing of evening study visit medication, there were no clinically relevant items that had an effect on the interpretation of the efficacy results of the study. No safety signals, emerged from the inspectional observations with this drug product, other than the tiotropium drug safety profile that is already known and well characterized. Dr. Tilles responded adequately to the List of Inspectional Observations on January 9, 2015.

From the discussions with the DPARP Medical Team, selected relevant examples that merit discussion from the List of Inspectional Observations are mentioned below:

(1) Investigation was not conducted in accordance with the investigational plan. Specifically,

- a. Per protocol the evening dose of the patient's own inhaled corticosteroids, leukotriene receptor antagonist [LTRA] (if applicable) and study medications should be administered within 30 minutes of the time of evening administration at Visit #2 and between 06:00 pm and 08:00 pm. In six out of eight subjects who completed the study, the evening dose of the trial medication was not administered per protocol. For example:
 - (i) Subject 4181727's Visit #4 evening dose on March 6, 2011 was given 146 minutes early; Visit #5 evening dose on April 26, 2011 was given 92 minutes late, and Visit #6 evening dose on June 21, 2011 was given 12 minutes late.
 - (ii) Subject 4181732's Visit #3 evening dose on May 3, 2011 was given 108 minutes late; Visit #4 evening dose on May 30, 2011 was given 113 minutes late.
 - (iii) Subject 4181739's Visit #3 evening dose on December 18, 2011 was given 28 minutes late; Visit #4 evening dose on January 22, 2012 was given 58 minutes late; Visit #5 evening dose on March 11, 2012 was given 43 minutes late, and Visit #6 evening dose on May 6, 2012 was given 88 minutes late.
- b. For five subjects on a total of 13 occasions, the times for PM doses of study medication were not reported the night prior to the clinic visit. Therefore, it was unclear if morning doses of medication on study visit days were taken within the correct timeframe.

- c. For five subjects, the morning dose of study medication (salmeterol or placebo metered dose inhaler) was taken after 8:00 AM on the day of study visit.
- d. For two subjects on a total of four occasions, the evening dose of study medication was taken after 8:00 PM on the evening prior to the study visit. By protocol, these subjects were to have their study visits rescheduled.

OSI Comment: As noted above, these observations were discussed with the review division. While these were protocol violations these observations were not considered to be critical to efficacy endpoint determination.

- e. Adverse events were not recorded on the eCRF. For example:
 - (i) Subject 4181729 had severe right heel pain. Onset and end dates were unknown, and the event was not recorded in the eCRF.
 - (ii) Subject 4181734 had sty excision with a September 19, 2011 onset and October 6, 2011 end date and was not recorded in the eCRF.

OSI Comment: The lack of source documentation of onset and end dates of these adverse events and failure to report these in the AE log and eCRF does not have any critical impact on the reported safety profile the study medication.

- f. For all the randomized subjects in this study (Subjects 4181726, 4181727, 4181728, 4181730, 4181732, 4181734, 4181736, 4181738. and 4181739), the study site did not record the time of administration of the inhaled corticosteroid (iCS) and the metered dose inhaler (MDI). There was no assurance that at each clinic visit, medication administration was conducted in a fixed sequence as per protocol.

OSI Comment: DPARP stated that these observations were not significant and had no impact on their efficacy evaluation of this NDA.

Per DPARP, corticosteroid inhalation (iCS) does not have an immediate broncholidatory effect; therefore, PFT measurements are not affected. However, in DPARP's evaluation, they would evaluate potential increases in the trough FEV1 as a surrogate measure for a reduction in asthma exacerbations. Worksheets supplied by the sponsor listed the order study medication was to be administered (i.e., iCS, MDI with salmeterol or placebo and Respimat® with tiotropium or placebo), but collected only information on timing of the Respimat® administered dose of study medication (also captured by the MasterScope® CT spirometer).

- g. For Subject 4181736 and Subject 4181726, eligibility verification was reviewed by the PI after the subjects were already randomized into the study.

OSI Comment: This was not a significant observation. Per Dr. Tilles' response, inclusion/exclusion criteria were verified by staff and PI prior to randomization, however, documentation (i.e., his signature) was not added until after randomization.

(2) Incomplete, inadequate and inaccurate case histories. Specifically,

- a. For Subject 4181739, source records noted an asthma exacerbation occurrence From February 17 to 18, 2012 and February 25-27, 2012. The eCRF recorded this event as February 7, 2012 to March 12, 2012.
- b. For Subject 4181739, Visit #6 on May 7, 2012 source records indicated that the study drug administration start time (19:08) and end time (19:09) were discrepant with the "Pulmonary Function Report" start time (20:08) and end time (20:09).

Dr. Tilles' written response to the Form FDA 483 was received on January 9, 2015. His response adequately addresses the observations and his site is working on developing Standard Operating Procedures (SOPs) or enhanced procedures to capture all necessary information, and enhanced training of staff for future studies.

c. Assessment of data integrity:

Many of the protocol violations at this site were related to the timing of study medication administration relative to their scheduled clinic visits. This was a four arm trial in which subjects were randomized to receive salmeterol or placebo MDI between 6 and 8 AM and salmeterol or placebo MDI and tiotropium or placebo Respimat® inhaler between 6 and 8 PM; clinic visits were scheduled for the PM administration. The protocols were designed with strict timelines, however the sponsor-provided materials like the e-diary and site worksheets were insufficient in terms of details recording critical time points. Information regarding the nature of the protocol deviations was discussed with DPARP who did not consider that the deviations were critical to overall efficacy endpoint assessment. Therefore, despite the above regulatory deficiencies, data submitted by this clinical site appear acceptable in support of this specific indication.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Two foreign clinical sites were selected for inspection in support of this application. Dr. Schmidt's site in Germany was inspected for Studies 205.416 and 205.419 and Dr. Quilodran's site in Chile was inspected for Study 205.444. A single domestic clinical site in Seattle, WA, Dr. Tilles, was selected for inspection for Study 206.418.

The final classification for Dr. Schmidt (Germany) is No Action Indicated (NAI). The preliminary classification for Dr. Quilodran (Chile) is Voluntary Action Indicated. The final classification for Dr. Tilles is Voluntary Action Indicated.

At both Dr. Quilodran's site for Study 205.444 and Dr. Tilles' site for Study 206.418, optimal drug sequencing associated with complexity of the study protocol (i.e., measuring PFTs prior to study drug administration and timing of administration of study medication in relationship to previous doses of medications) appeared to be problematic. Measurement of efficacy assessment following administration of study medication at the clinic visit was not, however, reported to be a problem. Specific protocol deviations from each site were discussed with the DPARP clinical review team who did not think that these would have significant impact on assessment of efficacy in their respective studies. Therefore, study data collected from these clinical sites appear reliable in support of the requested indication.

Note: The inspectional observations noted above for Dr. Quilodran is based on preliminary communications with the field investigator and/or preliminary review of the EIR. A clinical inspection summary addendum will be generated if conclusions on the current inspection report changes significantly, upon receipt of the Establishment Inspection Report (EIR). CDER OSI classification of inspection is finalized when written correspondence is issued to the inspected entity.

{See appended electronic signature page}

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/s/

ANTHONY J ORENCIA
03/31/2015

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SUSAN D THOMPSON
03/31/2015

Label and Labeling MEMORANDUM

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

Date of This Memorandum: February 6, 2015

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

Application Type and Number: NDA 207070

Product Name and Strength: Spiriva Respimat (Tiotropium Bromide) Inhalation Spray
[REDACTED] (b) (4)

Product Type: Single-Ingredient Product

Rx or OTC: Rx

Applicant/Sponsor Name: Boehringer Ingelheim

Submission Date: August 15, 2014

OSE RCM #: 2014-1959

1 PURPOSE OF MEMO

The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) requested that we review the proposed container labels, carton labeling, prescribing information, and instructions for use for Spiriva Respimat (Tiotropium Bromide) Inhalation Spray for risk of medication error (Appendix A) as part of their evaluation for NDA 207070, to determine if it is acceptable from a medication error perspective. We previously reviewed the labels under NDA 021936.¹ This product was submitted under NDA 207070 with a different indication (same product characteristics) than we previously reviewed. Since the previous NDA (021936) was not approved at the time, the Applicant was required to submit another NDA for the new indication.

2 CONCLUSIONS

The proposed container labels, carton labeling, prescribing information, and instructions for use are acceptable from a medication error perspective.

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

¹ Owens, Lissa. Label and Labeling Review for Spiriva Respimat (NDA 021936). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 July 14. 9 OSE RCM No.: 2014-753

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/s/

LISSA C OWENS
02/06/2015

KENDRA C WORTHY
02/06/2015

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

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

Application: NDA 207070

Application Type: New NDA (Type 9)

Name of Drug/Dosage Form: Spiriva Respimat

Applicant: Boehringer Ingelheim

Receipt Date: August 15, 2014

Goal Date: June 15, 2015

1. Regulatory History and Applicant's Main Proposals

Spiriva Respimat was approved for long-term, once-daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), and for reducing COPD exacerbations of COPD, NDA 21936, on September 24, 2014. Boehringer Ingelheim (BI) submitted on August 15, 2014, a new NDA application for Spiriva Respimat, NDA 207070, for the proposed indication of long-term, once-daily, add-on maintenance treatment of asthma in patients 12 years of age and older who remain symptomatic on at least inhaled corticosteroids, while NDA 21936 was under review.

2. Review of the Prescribing Information

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

3. Conclusions/Recommendations

No SRPI format deficiencies were identified in the review of this PI.

Appendix

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

Highlights

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

HIGHLIGHTS GENERAL FORMAT

Selected Requirements of Prescribing Information

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

Comment:

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

Comment:

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

Comment:

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

Comment:

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

Comment:

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

Comment:

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

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

Selected Requirements of Prescribing Information

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

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

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

Comment:

Highlights Limitation Statement

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

Comment:

Product Title in Highlights

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

Comment:

Initial U.S. Approval in Highlights

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

Comment:

Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

Comment:

- N/A** 13. The BW must have a heading in UPPER CASE, containing the word **“WARNING”** (even if more than one warning, the term, **“WARNING”** and not **“WARNINGS”** should be used) and other words to identify the subject of the warning (e.g., **“WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE”**). The BW heading should be centered.

Comment:

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

Comment:

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

Comment:

Selected Requirements of Prescribing Information

Recent Major Changes (RMC) in Highlights

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

Comment:

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

Comment:

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

Comment:

Indications and Usage in Highlights

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

Comment:

Dosage Forms and Strengths in Highlights

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

Comment:

Contraindications in Highlights

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

Comment:

Adverse Reactions in Highlights

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

Comment:

Selected Requirements of Prescribing Information

Patient Counseling Information Statement in Highlights

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

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

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

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

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

Comment:

Revision Date in Highlights

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

Comment:

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

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

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

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

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

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

Comment:

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

Comment:

Selected Requirements of Prescribing Information

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

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

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

Comment:

BOXED WARNING Section in the FPI

- N/A** 36. In the BW, all text should be **bolded**.

Comment:

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

Comment:

CONTRAINDICATIONS Section in the FPI

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

Comment: *Contraindications provided*

ADVERSE REACTIONS Section in the FPI

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

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

Comment:

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

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

YES

Selected Requirements of Prescribing Information

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

Comment:

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

Comment:

Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

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

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

[text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

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

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

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

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

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 [text]

2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 [text]

5.2 [text]

6 ADVERSE REACTIONS

6.1 [text]

6.2 [text]

7 DRUG INTERACTIONS

7.1 [text]

7.2 [text]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Labor and Delivery

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 [text]

14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

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

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
10/20/2014

LADAN JAFARI
10/20/2014

RPM FILING REVIEW

(Including Memo of Filing Meeting)

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

Application Information		
NDA # 207070 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Spiriva Respimat Established/Proper Name: tiotropium bromide Dosage Form: inhalation spray Strengths: (b) (4)		
Applicant: Boehringer Ingelheim Agent for Applicant (if applicable):		
Date of Application: 8/15/14 Date of Receipt: 8/15/14 Date clock started after UN:		
PDUFA Goal Date: 6/15/15		Action Goal Date (if different):
Filing Date: 10/14/14		Date of Filing Meeting: 9/25/14
Chemical Classification: (1,2,3 etc.) (original NDAs only) 9		
Proposed indication(s)/Proposed change(s): Asthma		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</i>		
Type of BLA	<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)	
<i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher or pediatric rare disease priority review voucher was submitted, review classification is Priority.</i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? X <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input checked="" type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): IND 46687, IND 65127				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:	<input type="checkbox"/>	<input type="checkbox"/>		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i></p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>																	
<p>Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</p> <p><i>Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</i></p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1482 1349 1623"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration													<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug</i></p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>																		

Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm				
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>) If yes, # years requested: The applicant only requested exclusivity but did not specify years. <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
For BLAs: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Format and Content	
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?	

<p>included with authorized signature per 21 CFR 54.4(a)(1) and (3)?</p> <p><i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p>				
Clinical Trials Database	YES	NO	NA	Comment
<p>Is form FDA 3674 included with authorized signature?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i></p> <p><i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Debarment Certification	YES	NO	NA	Comment
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>	<input type="checkbox"/>	<input type="checkbox"/>		
<u>Proprietary Name</u>	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<u>REMS</u>	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<u>Prescription Labeling</u>	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input checked="" type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide)			

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

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

	<input checked="" type="checkbox"/> Carton labels <input type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the PI submitted in PLR format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If representative labeling is submitted, are all represented SKUs defined?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

4

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

<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): June 9, 2008	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): December 9, 2013	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: 9/25/14

BLA/NDA/Supp #: NDA 207070

PROPRIETARY NAME: Spiriva Respimat

ESTABLISHED/PROPER NAME: tiotropium bromide inhalation spray

DOSAGE FORM/STRENGTH: (b) (4)

APPLICANT: Boehringer Ingelheim

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Asthma

BACKGROUND: BI submitted a new NDA application (NDA 207070) for Spiriva Respimat on August 15, 2014, received August 15, 2014, for the proposed indication of Asthma. NDA 21936, Spiriva Respimat, for COPD was still under review when NDA 207070 was received. Therefore, NDA 207070 is a Type 9 application.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Jessica Lee	Y
	CPMS/TL:	Ladan Jafari	N
Cross-Discipline Team Leader (CDTL)	A Durmowicz		Y
Clinical	Reviewer:	Stacy Chin	Y
	TL:	Tony Durmowicz	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Yunzhao Ren	Y
	TL:	Satjit Brar	Y
Biostatistics	Reviewer:	Kiya Hamilton	Y
	TL:	David Petullo	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Luqi Pei	Y
	TL:	Marcie Wood	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Jean Nashed	Y
	TL:	Julia Pinto	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers			
Other attendees	Nichelle Rashid		

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., BA/BE studies):</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA , include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input checked="" type="checkbox"/> YES Date if known: May 11, 2015 <input type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

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

<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>CMC Labeling Review</u></p> <p>Comments:</p>	<input type="checkbox"/> Review issues for 74-day letter
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days? 	<input checked="" type="checkbox"/> N/A <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	
<ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Badrul A. Chowdhury, MD, PhD	

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V):

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p><input checked="" type="checkbox"/> Standard Review</p> <p><input type="checkbox"/> Priority Review</p>

ACTIONS ITEMS

<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	<p>If priority review:</p> <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and

	the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
<input type="checkbox"/>	Other

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
10/20/2014

LADAN JAFARI
10/20/2014