

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
021936Orig1s000

OTHER REVIEW(S)

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

PATIENT LABELING REVIEW

Date: August 28, 2014

To: Badrul Chowdhury, MD, PhD
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)
Meeta Patel, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Instructions for Use (IFU)

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

Dosage Form and Route: Inhalation Spray

Application Type/Number: NDA 21-936

Applicant: Boehringer Ingelheim Pharmaceuticals, Inc.

1 INTRODUCTION

On March 24, 2014, Boehringer Ingelheim Pharmaceuticals, Inc. submitted for the Agency's review a New Drug Application Resubmission 2 for SPIRIVA RESPIMAT (tiotropium bromide) Inhalation Spray. The original New Drug Application was submitted on November 16, 2007. The agency issued a Complete Response Letter on September 16, 2008 due to clinical deficiencies. SPIRIVA RESPIMAT (tiotropium bromide) Inhalation Spray is indicated for the long term, once daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), and for reducing COPD exacerbations.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) on April 7, 2014, for DMPP and OPDP to review the Applicant's proposed Instructions for Use (IFU) for SPIRIVA RESPIMAT (tiotropium bromide) Inhalation Spray.

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

2 MATERIAL REVIEWED

- Draft SPIRIVA RESPIMAT (tiotropium bromide) Inhalation Spray IFU received on March 24, 2014 and received by DMPP on August 22, 2014.
- Draft SPIRIVA RESPIMAT (tiotropium bromide) Inhalation Spray IFU received on March 24, 2014, and received by OPDP on August 22, 2014.
- Draft SPIRIVA RESPIMAT (tiotropium bromide) Inhalation Spray Prescribing Information (PI) received on March 24, 2014, revised by the Review Division throughout the review cycle, and received by DMPP on August 22, 2014.
- Draft SPIRIVA RESPIMAT Prescribing Information (PI) received on March 24, 2014, revised by the Review Division throughout the review cycle, and received by OPDP on August 22, 2014.
- Draft STRIVERDI RESPIMAT (olodaterol) labeling submitted to the review division on June 23, 2014.

3 REVIEW METHODS

In 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We have reformatted the IFU document using the Verdana font, size 11.

In our collaborative review of the IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the IFU is consistent with the Prescribing Information (PI)
- ensured that the IFU is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the IFU is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The IFU is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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

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

/s/

SHARON W WILLIAMS
08/28/2014

MEETA N PATEL
08/28/2014

LASHAWN M GRIFFITHS
08/28/2014

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

Memorandum

****PRE-DECISIONAL AGENCY MEMO****

Date: August 28, 2014

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

From: Meeta Patel, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 021936
OPDP Comments for draft Spiriva Respimat (tiotropium bromide) PI,
carton/container, and IFU

OPDP has reviewed the proposed Spiriva Respimat (tiotropium bromide) PI and have the following comments. We have no comments on the carton/container labeling.

Thank you for the opportunity to comment on the proposed PI and carton/container. Comments on the proposed IFU has been submitted under separate cover in collaboration with DMPP.

If you have any questions or concerns, please contact Meeta Patel at 301-796-4284 or meeta.patel@fda.hhs.gov.

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

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

/s/

MEETA N PATEL
08/28/2014



Food and Drug Administration
Office of Device Evaluation
10903 New Hampshire Avenue
Silver Spring, MD 20993

NDA 21-936- Regulatory Device Consult

Addendum

Date: August 21, 2014

From: Amy LeVelle, Biomedical Engineer, RPDB/DAGRID/ODE/CDRH

Through: Deepika Lakhani, Ph.D. Combination Products Team Lead,
RPDB/DAGRID/ODE/CDRH
Anya Harry, M.D., Ph.D, RPDB Chief, DAGRID/ODE/CDRH
Tejashri Purohit-Sheth, M.D. Clinical Deputy Division Director
DAGRID/ODE/CDRH

To: Eugenia Nashed, PhD, CDER

Re: NDA 21-936 Spiriva Respimat (tiotropium bromide) Inhalation Spray

CDER requested an engineering device review of the Spiriva Respimat Inhalation Spray (NDA 21-936) submitted by Boehringer Ingelheim. Additional information was requested by CDRH regarding device malfunctions which were reported in the clinical studies. This addendum is to update the previous consult memo following a review of the sponsor's response.

Additional Information Request:

The following request was previously sent to the sponsor and the responses are discussed below.

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

implemented. Please clarify whether any of the corrective actions implemented required a modification in device design.

BI Response:

“A detailed description of the RESPIMAT inhaler malfunctions reported and of the corrective actions which were put in place, both for RESPIMAT A4 (used in Phase III studies) and for RESPIMAT A5 inhalers (used in Phase IIIb studies and proposed commercial use), has been provided in the Pharmaceutical Development Report [Document no. U13-2123-01 (ADD 2486), pages 159 – 185]. This report is contained in Module 3 of the NDA ((21-936), SEQ 0003, e-CTD section 3.2.P.2).

The RESPIMAT A5 inhaler differs from the RESPIMAT A4 inhaler only in that it includes a new design of the dose indicator (ensuring continuous feedback to the patient regarding the amount of available medication left for use), a locking mechanism and a product specific cap color. An aqua (turquoise) cap represents SPIRIVA RESPIMAT. The locking mechanism prevents the use of SPIRIVA RESPIMAT beyond the labeled number of doses.

The complaints received for the RESPIMAT A5 inhaler used in the large Phase IIIb studies (e.g., study 205.452) were different types of events (see Table 1) that had not been observed in the previous Phase III studies with the RESPIMAT A4 inhaler, indicating that the corrective actions taken for Respimat A4 as described in the aforementioned Pharmaceutical Development report have been successful.

An extremely high number of RESPIMAT A5 inhalers (more than 1,000,000 inhalers) have been used by patients in the SPIRIVA Phase IIIb clinical trials. Despite the large number of inhalers used in the study, only a very small percentage (less than 0.002%) were confirmed to be malfunctioning. For the malfunctioning inhalers, corrective actions have been implemented and continuous monitoring is in place during the manufacture of the RESPIMAT inhalers. Table 1 provides a summary of the types of confirmed malfunctions with the Respimat A5 inhalers and BI's corresponding corrective actions.”

The table below provides a summary of returned RESPIMAT A5 inhalers from Phase IIIb clinical studies.

Complaint no.	Description of complaint	Root cause analysis	Preventive action
<u>3/2007</u> <u>5/2007</u> <u>10/2007</u> <u>32/2007</u> <u>35/2007</u> <u>2/2008</u> <u>15/2008</u> <u>28/2008</u>	<p>The inhalers did not generate a spray from the first dose onwards or before the end of the labeled number of doses. The investigation showed that the cartridges did not contain enough inhalation solution to fully immerse the capillary tube.</p>	<p>A root cause analysis suggests that the capillary tube of the RESPIMAT inhaler may crack the shaft (diving tube) of the plastic cap if the patient uses excessive force during the insertion of the cartridge (causing leakage of the inhalation solution), such as hitting the bottom of the cartridge onto a hard surface. This is a clear deviation from the patient's instruction leaflet and represents a misuse of the drug product.</p>	<p>As a preventative measure, the outer geometry of the shaft of the plastic cap was changed. The new geometry eliminates a slight angle along the shaft length and does not impair the function or tightness of the plastic cap. This modification makes it less likely that excessive force during insertion of the cartridge will crack the shaft.</p> <p>This change was discussed with the FDA during an End-of-Review meeting for the COMBIVENT RESPIMAT NDA 021747 (dated January 25, 2010) and supporting data was included with the re-submission of the COMBIVENT RESPIMAT NDA which was approved on October 7, 2011.</p>
<u>4/2008</u> <u>6/2008</u>	<p>The cartridges were deformed. Thus, insertion of the cartridge or priming of the inhaler was difficult or not possible.</p>	<p>This was likely caused by the cartridge packaging/transport process.</p>	<p>As a preventative measure, the cartridge sorting equipment used in the packaging process was optimized to assure removal of deformed cartridges.</p>
<u>23/2008</u> <u>25/2008</u> <u>C-366-10</u> <u>C-745-11</u>	<p>The RESPIMAT inhalers did not dispense any spray or did not work properly after some doses.</p>	<p>The evaluation revealed a partial blockage of the Uniblock nozzle outlet. Based on the investigation this appeared to be a random event which is not indicative of a systemic problem.</p>	<p>Based on the investigation findings and the very low frequency of this event (over 1,000,000 units manufactured and used in the Phase IIIb studies), no preventative actions were taken. The defect rate of RESPIMAT inhalers is continuously monitored.</p>

C-481-12	The RESPIMAT inhaler did not generate a spray.	During the process of inserting the cartridge into the RESPIMAT inhaler, a piece of perforated tamper protection seal was pushed into the cartridge solution. The capillary tube was blocked by the piece of tamper protection seal so that no inhalation solution could be metered. The root cause was a worn plunger (b) (4) which had caused the perforation of the tamper protection seal.	An existing in-process control was adapted to (b) (4) prevent plunger wear and re-occurrence of this issue.
26/2006	The case bottom part of the RESPIMAT inhaler could only be removed with increased force.	It was found that the patient booklet label used with clinical trial supplies was fixed to the driving tube of the RESPIMAT inhaler and the dose counter of the inhaler, thus making it difficult to remove the case bottom part.	As a preventive measure for clinical packaging, the position of the booklet was moved to the case upper part of the RESPIMAT inhaler.

The sponsor indicates that “None of the corrective actions implemented required a modification of the inhaler design: the dose metering and nebulization system remained unchanged, and there is no change of the in vitro delivered dose or of the in vitro particle size distribution.”

Reviewer’s Comment: Response Adequate. *The sponsor has provided a detailed description of the reported malfunctions and complaints on pages 159-185 of the pharmaceutical development report. All malfunctioning RESPIMAT A4 devices and RESPIMAT A5 devices were returned from the clinical trials and fully investigated by the sponsor. When arriving in the laboratory all returned devices were checked, i.e., for intactness and apparent damage, cleanliness, position of the dose indicator, proper insertion of the cartridge, device locked or not locked. Additionally, according to each complaint appropriate tests were performed on the device, i.e., on priming behavior, pump delivery, dose delivery, delivered volume, particle size distribution by Andersen Cascade Impactor or laser diffraction, spray aberrations, cocking torque, movement of dose indicator, volume of the inhalation solution in the returned cartridge and appearance of the cartridge. If necessary, the device was disassembled and subassemblies or single components were inspected for irregular observations. All inhalers were found to show normal dosing characteristics. Complaints on the function of the dose indicator were assessed*

visually by checking position and movement of the indicator. All alleged malfunctioning dose indicators worked properly.

Most of the complaints had their origin in a lack of inhalation solution in the cartridge. The sponsor has implemented changes in the manufacturing/assembly in order to mitigate these issues. A root cause analysis suggested that the capillary tube of the RESPIMAT device may crack the shaft (diving tube) of the plastic cap if the patient uses excessive force during the insertion of the cartridge, such as hitting the bottom of the cartridge onto a hard surface. As a preventive measure, the outer geometry of the shaft has been changed for plastic caps manufactured since 2007. This change was provided in Amendment 5 dated Sept 7, 2007 to DMF # 17403 (Plastic Cap [REDACTED] (b) (4)). The new geometry eliminates a slight angle along the shaft length and does not impair the function or tightness of the plastic cap. This modification makes it less likely that excessive force during insertion of the cartridge will crack the shaft. This minor change is not a concern has been previously evaluated by FDA under NDA 021747 for Combivent Respimat.

The sponsor has taken adequate steps to investigate the root cause and mitigate the reported device malfunctions at this time. Therefore, the sponsor's response is adequate and I have no further questions.

I. Recommendation

The sponsor has adequately addressed the previous concerns and there are no outstanding device issues at this time.

Digital Signature Concurrence Table	
Reviewer Sign-Off	Amy K. Levelle -S 2014.08.21 15:47:10 -04'00'
Branch Chief Sign-Off	 Anya C. Harry -S 2014.08.27 10:41:41 -04'00'
Division Sign-Off	

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

/s/

JESSICA K LEE
08/28/2014
Signing on behalf of CDRH reviewer



DEPARTMENT OF HEALTH AND HUMAN SERVICES M E M O R A N D U M

Food and Drug Administration
Office of Device Evaluation
10903 New Hampshire Avenue
Silver Spring, MD 20993

NDA 21-936

Response to Device Consult Request

Date: July 11, 2014

From: Amy LeVelle, Biomedical Engineer, RPDB/DAGRID/ODE/CDRH

Through: Deepika Lakhani, Combination Products Team Lead, RPDB/DAGRID/ODE/CDRH
Anya Harry, M.D., Ph.D, RPDB Chief, DAGRID/ODE/CDRH
Tejashri Purohit-Sheth, M.D. Clinical Deputy Division Director DAGRID/ODE/CDRH

To: Eugenia Nashed, PhD, CDER

Re: NDA 21-936 Spiriva Respimat (tiotropium bromide) Inhalation Spray

I. Summary

CDER has requested an engineering device review of the Spiriva Respimat Inhalation Spray (NDA 21-936) submitted by Boehringer Ingelheim. The proposed indication is for once-daily use, in a long-term maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema.

The same device is a part of an approved combination product, Combivent Respimat, NDA 21-747, already on the market. Additionally, an NDA (NDA 21-936) for Spiriva Respimat was originally filed in 2007 and a device review was previously conducted by CDRH. Agreements between Boehringer Ingelheim and FDA were reached on all CMC questions that arose during review of the 2007 NDA. FDA's Complete Response Letter of September 16, 2008 had no CMC deficiency comments to address. This is a resubmission of the same device.

Since the time between FDA's response letter of September 16, 2008 and the resubmission of this NDA, the CMC documentation as agreed between Boehringer Ingelheim and FDA during review of the 2007 NDA has been modified. The primary differences were related to the drug formulation and manufacturing, with only minor differences in device design as detailed further in the memo below.

RECOMMENDATION: *There are no outstanding concerns regarding the design modifications reported since CDRH completed the previous review of this device in 2008. However, additional information is recommended to be requested regarding the device malfunctions reported in the clinical studies.*

II. Device Description

The product SPIRIVA RESPIMAT consists of a sterile aqueous inhalation solution of tiotropium bromide monohydrate in a cartridge and a RESPIMAT inhaler. The principle of the RESPIMAT inhaler is to meter a small volume of the inhalation solution and to press it through a nozzle with two fine outlets. Two solution jets are formed that impinge on and nebulize each other, resulting in the spray which is inhaled by the patient.

The cartridge with the inhalation solution and the RESPIMAT inhaler are supplied as two entities in one package. Prior to first use, the patient inserts the cartridge into the inhaler. Figure 1(left) shows the RESPIMAT inhaler with the cartridge inserted and the aerosol generated; the cartridge alone is shown in Figure 1 (right).

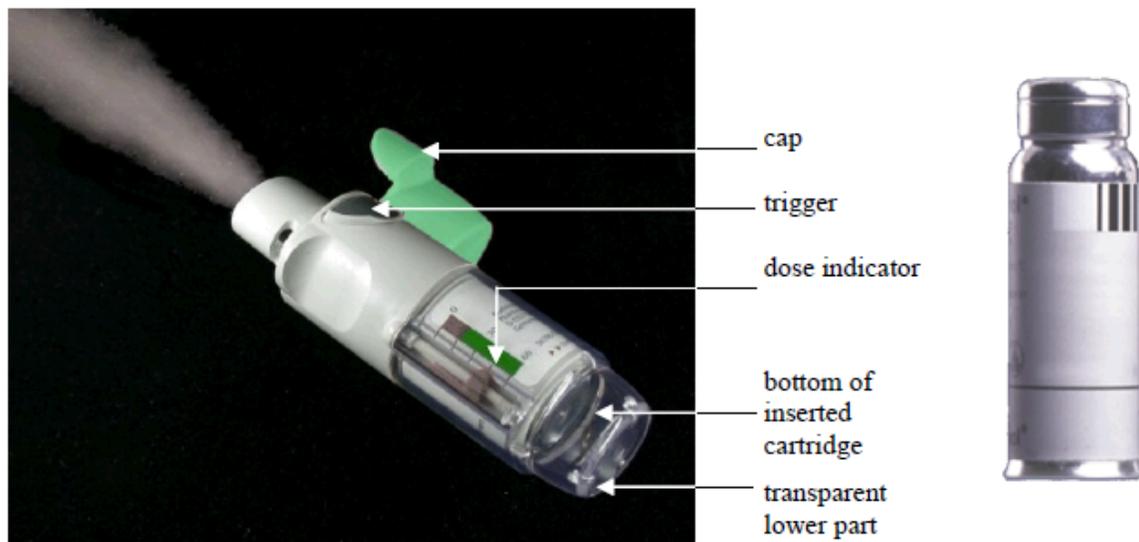


Figure 1: RESPIMAT Inhaler and Cartridge

Dosing:

The product strength is 2.5 µg tiotropium per actuation. One dose consists of two actuations, resulting in 5 µg tiotropium per dose. The recommended dose regimen for SPIRIVA RESPIMAT is 1 dose per day consisting of two actuations.

The device is single patient reusable up to a period of 3 months and marketed with two versions, consisting of a 60 actuation (30 dose) and a 28 actuation (14 dose) size. The 28 actuation size is proposed for hospital administration and for physician samples to introduce the drug product to the patients. The difference between the sizes consists only in the set up for the locking mechanism of the inhaler. After preparation for use, the locking mechanism for the 28 actuation size is set to lock the inhaler after 28 actuations of patient use (14 day therapy), whereas the 60 actuation size locks the inhaler after 60 actuations of patient use (1 month therapy). The cartridge system for both the “60 actuation size” and “28 actuation size” is identical with each containing at least 4.0 mL of inhalation solution. Only one cartridge per inhaler is used and the inhaler is therefore disposable.

When used with SPIRIVA, the RESPIMAT inhaler meters and nebulizes a volume of (b) (4) solution (= metered volume per dose [two actuations]). During the nebulization process, some of the generated aerosol deposits on the inner surface of the mouthpiece. Due to this mouthpiece retention, the delivered volume is smaller than the metered volume; it is 22.1 µL for SPIRIVA.

Respimat System:

The sponsor indicates the main targets of the RESPIMAT device development were:

- propellant-free system
- high *in vitro* fine particle fraction
- user friendliness, *i.e.*, easy inhalation procedure by simple co-ordination between actuation and inhalation

The basic principle of the RESPIMAT inhaler is to press a metered volume of inhalation solution through a nozzle (“uniblock”) with two outlets (outlet size: $\varnothing^{(b)}(4)$). Each outlet forms a jet of solution. The two outlets are arranged in such a way that the two solution jets converge on each other; the aerosol cloud is created by this collision. The metered volume is provided by a pressure differential: A tube (“capillary tube”) moves like a piston in a second tube (“central tube”). The capillary tube is firmly connected at its lower end to the cartridge with the solution for inhalation. The central tube is firmly connected at its upper end to the uniblock with the nozzle outlets. By turning the transparent lower part of the inhaler by 180°, the capillary tube is drawn back within the central tube. This forms the metering chamber in the central tube and creates a low pressure there, sucking the solution for inhalation through the capillary tube into the metering chamber.

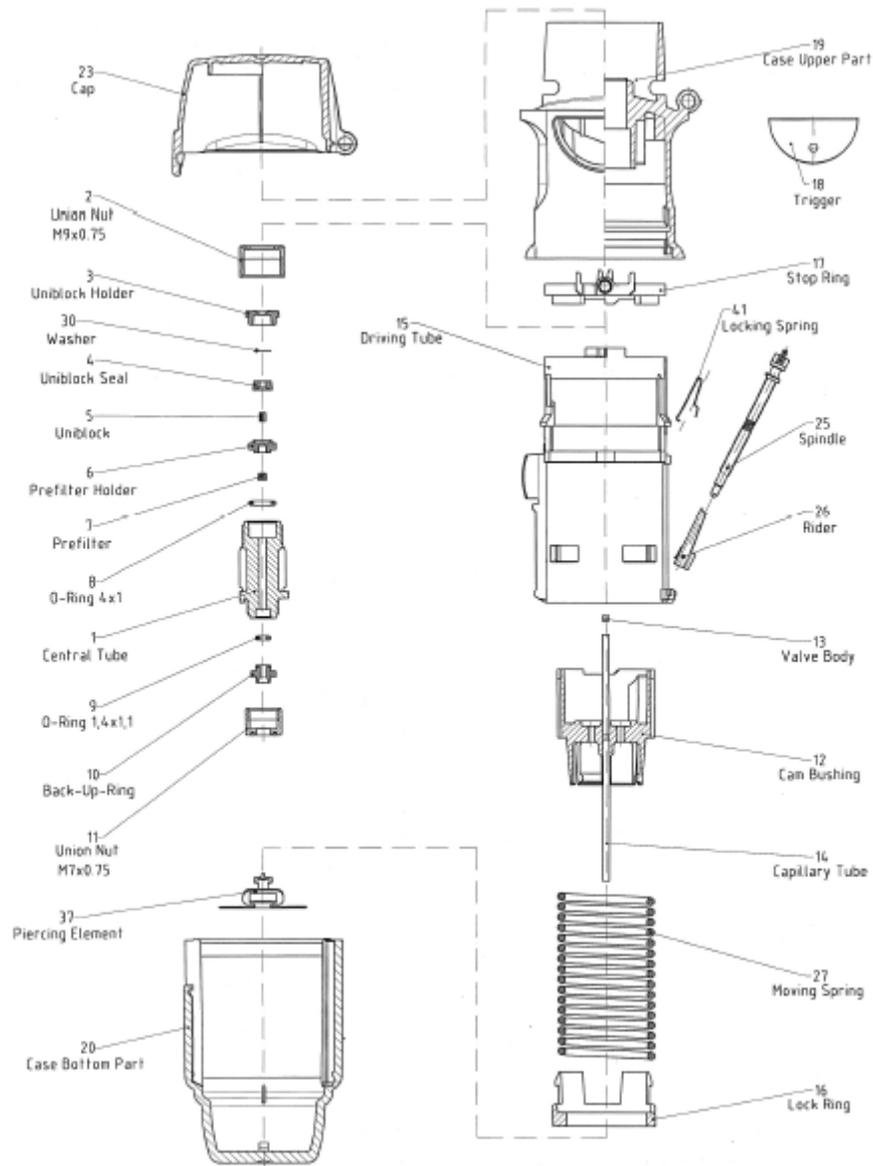


Figure 2: RESPIMAT Schematic

Turning the lower part of the inhaler by 180° not only provides and fills the metering chamber, but at the same time compresses a spring and moves the trigger button outwards. Pressing the trigger for an actuation releases the spring; this drives the capillary tube back to its original position and forces the solution out of the metering chamber through the uniblock: two jets of solution are formed which impact each other and form the aerosol cloud. When the patient again turns the lower part of the RESPIMAT, the next spray can be released by pressing the trigger.

The nebulization takes about (b) (4) seconds. The duration of the spray facilitates co-ordination of release of the aerosol and inhalation which for pMDIs often has been reported as difficult. Therefore, the spray duration is advantageous.

Dose Indicator

The RESPIMAT inhaler has a dose indicator. The dose indicator is combined with a mechanical locking mechanism that locks the RESPIMAT inhaler to prevent further use when the labeled number of doses has been reached. After locking, it is no longer possible to turn the lower part of the inhaler, rendering the RESPIMAT inhaler unusable. The locking mechanism has no effect until after the administration of the last dose.

Being a novel device, the RESPIMAT was developed with several interim versions and was not available in its final version from the very beginning of the product development. Specifically for SPIRIVA RESPIMAT, two versions of the device are of importance:

- the RESPIMAT version A4 – it has been used in the Phase III clinical studies (study nos. 205.249, 205.250, 205.251, 205.252, 205.254, and 205.255) prior to the 2007 NDA submission, which demonstrate the safety and efficacy and serve as basis for the dose selection (see CTD Module 2.5: Clinical Overview), and in supportive stability studies
- the RESPIMAT version A5, which is intended for the commercial product; it has been used in primary stability studies and in later clinical studies (e.g., studies 205.372, 205.458 and 205.452)

The key development step from RESPIMAT A4 to RESPIMAT A5 was the inclusion of a locking mechanism to lock the RESPIMAT A5 after the labeled number of doses. Further changes between the two versions are merely cosmetic (e.g., change in cap color). Neither uniblock nor the cartridge system nor the composition of the solution was changed.

III. Discussion

The same device is a part of an approved combination product, Combivent Respimat, NDA 21-747 already on the market. In addition, an NDA (NDA 21-936) for Spiriva Respimat was originally filed in 2007 and a device review was previously conducted by CDRH in 2008. The previous CDRH reviewer was Mr. Sugato De and he had no major outstanding device issues. Therefore, this review will focus primarily on the modifications which have been made to the device since submission of the previous NDA.

Since the time between FDA's response letter of September 16, 2008 and the resubmission of this NDA, the CMC documentation as agreed between Boehringer Ingelheim and FDA during review of the 2007 NDA has been modified. Below is brief overview of the key changes:

- The 2007 NDA submission referred to tiotropium bromide monohydrate drug substance as described in Boehringer Ingelheim's Type II DMF #18135. Since the original NDA submission, a new route of synthesis (transacyl process) for the manufacture of the drug substance has been introduced to address worker safety issues. This new route of synthesis for tiotropium bromide monohydrate is described in Boehringer Ingelheim's Type II DMF #21939. The DMF has been

reviewed by FDA for inclusion into the NDA for Spiriva[®] HandiHaler[®] (tiotropium bromide Inhalation Powder; NDA 21-395). Spiriva[®] Respimat[®] now makes reference to DMF #21939 instead of DMF #18135.

- Additional drug product stability data are provided, and a shelf-life of the drug product of 36 months instead of (b) (4) is proposed. The additional stability data include 36 months stability data of the drug product manufactured with tiotropium bromide monohydrate following the (b) (4) described in DMF #21939.
- The market/trade presentations for SPIRIVA RESPIMAT will have – in addition to the already submitted 30 dose inhaler (which delivers 30 doses and locks after that) – a 14 dose inhaler size, which delivers and locks after 14 doses. The 14 dose size is proposed for hospital administration and for physician samples to introduce the drug product to the patients. The difference between the sizes consists only in the set up for the locking mechanism of the inhaler.
- Information on the container closure system has been re-organized in two new Type III DMFs: a DMF for the RESPIMAT Inhaler (DMF #26015) and a DMF for the Container Closure for RESPIMAT Aqueous Solutions (DMF #26014). References to these DMFs replace the 2007 references to DMF #17322 (RESPIMAT Inhaler) and to DMF #17403 (Plastic Cap (b) (4)) and capture the RESPIMAT container closure information (*i.e.*, manufacturing, sterilization of the cap/container and controls) previously presented in the original SPIRIVA RESPIMAT NDA submission. The new DMFs have been reviewed by FDA in the context of STRIVERDI (Olodaterol) RESPIMAT Inhalation Spray (NDA 203108) and of the COMBIVENT RESPIMAT NDA (21-747) by a CBE 30 Day Supplement (July 12, 2012).
- Several modifications have been made to the testing specifications for the drug product.
- For sterility testing of the drug product, the sterility testing laboratory (b) (4) has been included.
- Further minor modifications included
 - addition of new analytical drug product batch data,
 - update of the drug product manufacturing documentation to reflect a higher yield and to provide more details for batch sizes between the minimum and maximum size
 - continued reporting of monitoring data of the (b) (4) manufacture of the drug product
 - inclusion of development information into the Pharmaceutical Development Report on a lower strength of the drug product (1.25 µg tiotropium per actuation) which has been used in clinical phase III studies
 - update of the Justification of Specification reports for the Drug Product to reflect the agreements reached between FDA and Boehringer Ingelheim during review of the 2007 NDA.

Three new clinical studies are described in Module 5 in this resubmission dossier: Study 205.458 (Phase IIb), 205.372 (Phase IIIb), and 205.452 (Phase IIIb). Since a lower dose strength (1.25 µg per actuation, 1 dose = 2 actuations) of SPIRIVA RESPIMAT Inhalation Spray was investigated in the large long term Phase IIIb study (205.452), supporting CMC documentation on this dose strength is included for completeness in Module 3.

Reviewer's Comment: The primary changes for this NDA submission were related to the drug product, including changes in the manufacturing of the drug substance, drug product specifications and drug stability data. The only significant change in device design reported was regarding the locking mechanism. The sponsor will now offer a 14 dose inhaler in addition to the

already submitted 30 dose inhaler (which delivers 30 doses and locks after that). The 14 dose size is proposed for hospital administration and for physician samples to introduce the drug product to the patients. The difference between the sizes consists only in the set up for the locking mechanism of the inhaler. After preparation for use, the locking mechanism for the 28 actuation size is set to lock the inhaler after 28 actuations of patient use (14 day therapy), whereas the 60 actuation size locks the inhaler after 60 actuations of patient use (1 month therapy). The cartridge system for both the “60 actuation size” and “28 actuation size” is identical with each containing at least 4.0 mL of inhalation solution.

A change in the locking mechanism would not be expected to affect the output performance or aerosol. The sponsor has conducted verification testing in order to confirm that the locking mechanism functions as intended. The device modifications are minor and do not introduce any new concerns from the design perspective.

Device complaints and malfunctions:

The SPIRIVA clinical phase III studies used approximately (b) (4) RESPIMAT A4 inhalers. Only 22 relevant malfunctioning inhalers could be confirmed. In 14 of these 22 cases the cartridge did not contain enough solution to deliver the doses. The other complaints were caused by assembly errors or individual failures. Corrective actions have been implemented to prevent the defects with future batches. In the Berodual® study, no malfunctioning RESPIMAT A5 inhalers at all were reported out of approximately 250 inhalers used. Finally, large Phase IIIb studies conducted with SPIRIVA RESPIMAT (e.g., study 205.452) after the 2007 NDA submission used more than 1,000,000 RESPIMAT A5 inhalers. Out of these, only 16 complaints could be confirmed. This results in a percentage of justified complaints of less than 0.002% of all used RESPIMAT A5 devices. Comparing the incidence rates of justified complaints for RESPIMAT A4 devices with RESPIMAT A5 devices the percentage is reduced from < 0.2% down to < 0.002%. The sponsor indicates that this minimization shows that preventive actions were successful and led to an improved device quality.

Reviewer’s comment: The sponsor has provided very limited information regarding the types of malfunctions which have been reported or corrective actions implemented. It is unclear whether any of the reported malfunctions might be related to design issues. The complaint rate is relatively low. However, if this modified device is approved as a combination product it will be expanded to a much larger population and the sponsor should attempt to mitigate all device malfunctions within reasonable means. I recommend additional information is requested regarding the reported device malfunctions and complaints (see comment to sponsor below).

IV. Recommendation

There are no outstanding concerns regarding the design modifications reported since CDRH completed the previous review of this device in 2008. However, additional information is recommended to be requested regarding the device malfunctions reported in the clinical studies.

The following request is recommended to be sent to the sponsor regarding device malfunctions:

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

discussion of all malfunctions and complaints reported as well as the mitigation strategies implemented. Please clarify whether any of the corrective actions implemented required a modification in device design.

Digital Signature Concurrence Table	
Reviewer Sign-Off	Amy K. Levelle -S 2014.07.14 10:32:24 -04'00'
Combination Product Team Lead Sign-Off	Deepika A. Lakhani -A 2014.07.14 11:55:43 -04'00'
Branch Chief Sign-Off	 Anya C. Harry -S 2014.07.14 10:37:44 -04'00'
Division Sign-Off	 Tejashri S. Purohitsheth -S Clinical Deputy Director DAGRID/ODE/CDRH 2014.07.14 11:42:00 -04'00'

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

07/15/2014

Signed on behalf of CDRH reviewer

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:	July 14, 2014
Requesting Office or Division:	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Application Type and Number:	NDA 021936
Product Name and Strength:	Spiriva Respimat (Tiotropium Bromide) Inhalation Spray 2.5 mcg per actuation
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Boehringer Ingelheim
Submission Date:	March 24, 2014
OSE RCM #:	2014-753
DMEPA Primary Reviewer:	Lissa C. Owens, PharmD
DMEPA Team Leader:	Kendra Worthy, PharmD
DMEPA Associate Director:	Lubna Merchant, M.S., PharmD

1 REASON FOR REVIEW

This review evaluates the proposed container labels, carton labeling, prescribing information, and instructions for use for Spiriva Respimat (Tiotropium Bromide) Inhalation Spray for risk of medication error in response to a request from the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP). DPARP requested this as part of their evaluation for NDA 021936.

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.

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

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Tiotropium Bromide is currently marketed as capsules for inhalation. The Respimat device is currently marketed with another product (Combivent Respimat). We did not retrieve any errors related to label and labeling with the currently marketed Tiotropium Bromide capsules for inhalation or the currently marketed Respimat device. The majority of errors that occur with the currently marketed Spiriva HandiHaler are related to wrong route in which patients accidentally swallow the capsules. The proposed Respimat device eliminates the need for the inhalation capsules being packaged separately and therefore will help to alleviate these wrong route errors.

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

also compared the label and labeling of Spiriva Respimat to Combivent Respimat to ensure that they are well differentiated from each other.

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

4 CONCLUSION

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

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Spiriva Respimat that Boehringer Ingelheim submitted on March 24, 2014.

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

APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

B.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on April 18, 2014 using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter.²

Date Range	May 13, 2011 to April 18, 2014 (Spiriva) May 22, 2012 to April 18, 2014(Combivent Respimat)
Product	Spiriva Combivent Respimat
Event (MedDRA Terms)	Medication Errors [HLGT] Product Packaging Issues [HLT] Product Label Issues [HLT] Product Quality Issues (NEC)[HLT]

B.2 Results

Our search identified 9193 cases of Spiriva and 6 cases of Combivent Respimat; none of the cases were evaluated further as they described lack of therapeutic effect, labeled adverse reaction, product complaints, and wrong route not relevant to this inhaler device (patients swallowing Spiriva capsules). None of the cases retrieved described a medication error related to label and labeling

B.4 Description of FAERS

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

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

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,¹ along with postmarket medication error data, we reviewed the following Spiriva Respimat labels and labeling submitted by Boehringer Ingelheim on March 24, 2014.

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

G.2 Label and Labeling Images



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

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

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

/s/

LISSA C OWENS
07/14/2014

KENDRA C WORTHY
07/14/2014

LUBNA A MERCHANT
07/14/2014

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 21936

Application Type: Class 2 NDA Resubmission

Name of Drug/Dosage Form: Spiriva Respimat (tiotropium bromide)

Applicant: Boehringer Ingelheim

Receipt Date: March 24, 2014

Goal Date: September 24, 2014

1. Regulatory History and Applicant's Main Proposals

NDA 21936 is a Class 2 Resubmission received March 24, 2014 as a Complete Response (CR) to the CR action dated, September 16, 2008. The resubmission addresses the two clinical deficiencies indicated in the CR action letter.

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

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant in an advice letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by May 23, 2014. The resubmitted PI will be used for further labeling review.

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 and HORIZONTAL LINES IN THE PI

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 (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (e.g., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is one-half page or less, then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period:**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of-Cycle Period:**

- Select “YES” in the drop down menu if a waiver has been previously (or will be) granted by the review division in the approval letter and document that waiver was (or will be) 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:

- NO** 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: *White space between product title and initial US Approval*

- 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

Selected Requirements of Prescribing Information

• 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

* 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

Selected Requirements of Prescribing Information

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

Comment:

- 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:

Recent Major Changes (RMC) in Highlights

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

Comment:

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

Comment:

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

Comment:

Indications and Usage in Highlights

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

Comment:

Dosage Forms and Strengths in Highlights

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

Comment: *One dosage form.*

Contraindications in Highlights

YES

Selected Requirements of Prescribing Information

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

Comment:

Adverse Reactions in Highlights

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

Comment:

Patient Counseling Information Statement in Highlights

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

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

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

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

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

Comment: *Has Instructions for Use*

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: *Contraindication is listed.*

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: *Appropriate modification*

- 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: *appropriate modification*

PATIENT COUNSELING INFORMATION Section in the FPI

- NO** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

Selected Requirements of Prescribing Information

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

Comment: *The type of FDA-approved patient labeling not included (Instructions for Use)*

- 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]
- [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

- 1.1 [text]
- 1.2 [text]

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
05/02/2014

LADAN JAFARI
05/02/2014

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: July 31, 2008

TO: Miranda Raggio, Regulatory Project Manager
Theresa Michele, Medical Officer

FROM: Jean Mulinde
Good Clinical Practice Branch II
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief, Good Clinical Practice Branch II
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 21-936

APPLICANT: Boehringer Ingelheim Pharmaceuticals, Inc.

DRUG: Spiriva®/Respimat® (Tiotropium bromide inhalation spray)

NME: No

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Long-term, once daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema COPD

CONSULTATION REQUEST DATE: January 10, 2008

DIVISION ACTION GOAL DATE: September 2, 2008

PDUFA DATE: September 16, 2008

I. BACKGROUND:

Boehringer Ingelheim Pharmaceuticals, Inc. seeks approval of tiotropium bromide inhalation spray delivered with the RESPIMAT device (a hand-held, pocket-sized, multi-dose, oral inhalation device that generates a slow-moving aerosol cloud of medication from the aqueous solution) for the maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD). A product containing the same drug substance, tiotropium bromide monohydrate, was previously approved for use as an inhalation powder with the HANDIHALER inhalation device (dry powder inhaler), [NDA 21-395, approved January 30, 2004].

This NDA contains the following four pivotal studies submitted in support of the requested indication. These trials are grouped into two sets of two replicate protocols.

- 205.251 and 205.252: 12-week comparison of the safety and efficacy of tiotropium/Respimat (5 mcg and 10 mcg) to ipratropium bromide (active comparator) and placebo in patients with COPD. The primary endpoint for these studies was trough FEV₁ at 12 weeks. Study 205.251 enrolled a total of 361 subjects and was conducted at 39 different centers in 4 ex-US countries (Germany, Italy, Switzerland, and South Africa). Study 205.252 enrolled a total of 358 subjects and was conducted at 25 different centers in the U.S. and Canada.
- 205.254 and 205.255: 48 week comparison of the safety and efficacy of tiotropium/Respimat (5 mcg and 10 mcg) to placebo in patients with COPD; additional vital status information on prematurely withdrawn patients is listed under protocol 205.392 (see note below). The primary endpoint for these studies was trough FEV₁ at 48 weeks. In addition, combined data from these studies is being used to support a labeling claim that Spiriva Respimat decreases COPD exacerbations (frequency and time to first exacerbation). Study 205.254 enrolled 983 subjects and was conducted at 77 different centers in 14 countries (Europe and North America). Study 205.255 enrolled 1007 subjects and was conducted in 79 different centers in 15 countries (Europe, North American, Africa, and Australia).

[Note: A mortality signal was observed in the 48-week studies in favor of placebo. This issue was discussed at an advisory board meeting of the Drug Safety Oversight Committee and also with the sponsor at a Type A meeting. It was determined in these meetings that no safety signal existed for Spiriva Handihaler (a marketed product) and additional follow up data should be gathered on patients with early discontinuations from the 205.254 and 205.255 trials to determine if differential discontinuation may have been a confounding factor. These follow up data are under protocol 205.392.]

The Clinical Investigators (CI) chosen for inspection were two centers that were high enrollers across multiple studies, Drs. Shmelev and Miller. In addition, a potential mortality signal was identified in this program, requiring additional safety review. In choosing sites for audit, no outliers were identified with regard to financial disclosure, protocol violations, or site specific efficacy. Sites in Russia, however, were notable for having all of the unexplained deaths in the study (safety signal). Dr. Shmelev was the second highest enroller for the pivotal 48 week Study 205.254, with 48 subjects. In addition, this site had the largest number of unexplained deaths in the study (4 deaths, 3 of which were unexplained). All deaths occurred in tiotropium Respimat groups.

Dr. Miller was the highest enroller for the pivotal 12 week Study 205.252, with 27 subjects. In addition, this site was also the highest US enroller for the pivotal 48 week Study 205.255, with 27 subjects.

II. RESULTS (by Site):

Name of CI City, State or Country	Protocol # # of Subjects	Inspection Dates	Interim Classification NAI/VAI/ OAI	Final Classification NAI/VAI/ OAI/ Pending
K. Scott Miller, M.D. Lowcountry Lung and Critical Care PA 9150-B Medcom St. Charleston, SC 29406-7108	Protocol #205.252 Site #12 Subjects: 27 Protocol #205.255 & 205. 392 Site #01512 Subjects: 27	03/20/2008- 04/09/2008	VAI	VAI
Eugene Shmelev, M.D. City Hospital NII 6 Dvintsev Str 127018 Moscow, Russia	Protocol #204.255 & 205. 392 Site #07402 Subjects: 48	03/31/2008- 04/04/2008	VAI	VAI

Key to Classifications

NAI = No deviation from regulations.

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

VAI-R = Response Requested = Deviation(s) from regulations.

OAI = Significant deviations from regulations.

Pending = Preliminary classification based on information in 483; EIR has not been received from the field and complete review of EIR is pending.

1. K. Scott Miller, MD

Lowcountry Lung and Critical Care
PA 9150-B Medcom St.
Charleston, SC 29406-7108
(Protocol #205.252, Site #12)
(Protocol #205.255 & 205. 392, Site #01512)

a. What was inspected:

This inspection was conducted in accordance with Compliance Program 7348.811 between 03/20/2008-04/09/2008. For Protocol #205.252, Site #12, a total of 38 patients were screened, 27 were randomized, and 25 completed the study. The inspection evaluated 100% of informed consent forms and comparison of source documents to CRFs for 15 study patients. Patient files were reviewed for verification of: 1) reported FEV₁, 2) inclusion and exclusion criteria, 3) safety and efficacy endpoint measurements, 4) adverse events, 5) serious adverse events, and 6) concomitant medications. In addition, drug accountability records, IRB approval and dates, and sponsor monitoring records were reviewed.

For Protocols 205.255/205.392, Site #01512, a total of 28 patients were screened, 27 were randomized, and 21 completed the study. The inspection evaluated 100% of informed consent forms and comparison of source documents to CRFs for 15 study patients. Patient files for Protocol 205.255 were reviewed for verification of: 1) reported FEV₁, 2) inclusion and exclusion criteria, 3) safety and efficacy endpoint measurements, 4) adverse events, 5) serious adverse events, 6) Mahler TD1 scores, 7) COPD Severity Scores, 8) Patient's Global Ratings and Physician's Global Ratings, and 9) concomitant medications. In addition, drug accountability records, IRB approval and dates, and sponsor monitoring records were reviewed.

For Protocol 205.392 specifically, the audit found that 4 of 6 patients who withdrew from the study were evaluated; the two patients that were not evaluated included Subject #8153 (was deceased and the site could not locate next of kin) and Subject #8158 who was lost to follow-up. Data points for vital status, demographics, and medication listings were compared to source documents and considered accurate.

There were no limitations to the inspection.

b. General observations/commentary:

In general, the study was conducted appropriately; however, some regulatory violations were documented and a Form FDA 483, Inspectional Observations, was issued to this investigator for:

1. Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the inspection. [21 CFR 312.62 (b)].
 - i. For Protocol 205.252
 - For 2 of 15 subject records reviewed, all non-serious adverse events recorded on the "Patient Daily Record" worksheets were not also captured on the "Adverse Events Worksheet, Cumulative (Visits 1-7)" page of the CRF.
 - For 1 of 15 subject records reviewed, patient reported Medical History/Concomitant Diagnoses were not captured in the CRF Visit 1 "Relevant Medical History/Concomitant Diagnoses" page of the CRF.
 - ii. For Protocol 205.255
 - In 2 of 15 subject COPD Severity Score records that were reviewed, there were single isolated discrepancies between information recorded on source document worksheets and the CRF.
 - For 2 of 15 subject records reviewed, all patient reported Medical History/Concomitant Diagnoses noted on source document worksheets were not captured in the CRF Visit 1 "Relevant Medical History/Concomitant Diagnoses" page.
 - For 1 of 15 subject records reviewed, concomitant medications documented on source documents were not listed in the CRF (use of pre-operative Versed and Fentanyl).

c. Assessment of data integrity:

While there was some underreporting of adverse events by the site, all serious adverse events were appropriately reported. Other observations made by the FDA inspector related to several instances of failure to document an item on the medical history, failure to report concomitant medication use, and isolated discrepancies between source documents and CRF COPD Severity Scores are considered minor and unlikely to significantly impact key endpoint analyses. Of note, the FDA inspector identified one instance of a value for FEV₁ being listed by the Applicant on the NDA line listing (Listing 6.1.2 FEV1 individual time point data) for which there was no source data available at the site and for which source data available suggested that a pulmonary function test was not done at that time point (patient #8114, Visit 9, 0.05 minute assessment). However, it is unlikely that these findings would affect data integrity. In general, based on the provided Establishment Inspection Report (EIR) for this site, data derived from Dr. Miller's site are considered acceptable.

2. Eugene Shmelev, MD

City Hospital N11
6 Dvinsev Str
127018 Moscow, Russia
(Protocol #204.255 & 205. 392, Site #07402)

a. What was inspected:

This inspection was conducted in accordance with Compliance Program 7348.811 between 04/17/2008-04/23/2008. For Site 07402 a total of 48 patients were screened, 42 were randomized, and 37 completed the study. One patient (#3409) was lost to follow-up and four patients died during the study (According to the official reports of death available in source records, Subject #4025 died of acute heart failure and hypertensive crisis, Subject #4047 died of acute heart failure and atherosclerosis, and Subject #4050 died of COPD. Subject #4041 died of myocardial infarction, according to the autopsy report available in source records). The inspection evaluated informed consents for all subjects. Data listings and case report forms for 11 of 42 randomized subjects were compared to source documents (including all 5 patients that discontinued early from study); this audit included verification of: 1) inclusion and exclusion criteria, 2) results of pulmonary function testing, 3) adverse events, 4) serious adverse events, 5) death reporting, 6) subject discontinuation (when present), and 7) outcome data for primary endpoint. In addition, drug accountability records and IRB approval and dates. There were no limitations to the inspection.

b. General observations/commentary:

In general, the study was conducted appropriately. However, a Form FDA 483, Inspectional Observations, was issued to this investigator for:

1. Failure to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].

The protocol specified in Section 6.2.3 that "PFTs (FEV1 and FVC) will be performed pre-dose (-10 minutes prior to test-drug inhalation) and at 5, 30 and 60 minutes and at 2

and 3 hours after inhalation of study medication.” For two subjects the protocol defined timeframes for obtaining pulmonary function tests (PFT) were not adhered to and adequate documentation of the reasons for variances were not documented.

2. Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the inspection. [21 CFR 312.62 (b)].

For failure to maintain any type of record (e.g. temperature logs) to show the actual storage conditions for the study medication.

d. **Assessment of data integrity:**

Although some regulatory violations were noted, it is unlikely that they would affect data integrity. Based on the provided Establishment Inspection Report (EIR) for this site and Dr. Shmelev’s responses regarding EIR Observations made during the inspection, which are documented in the EIR, data derived from Dr. Shmelev’s site are considered acceptable.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

In general, the studies appear to have been conducted adequately and the data in support of the NDA appear reliable. Final classifications of Clinical Investigator inspections of Dr. Miller and Dr. Shmelev are Voluntary Action Indicated (VAI). Safety and efficacy data from these clinical investigators is considered reliable.

{See appended electronic signature page}

Jean M. Mulinde, M.D.
Good Clinical Practice Branch II
Division of Scientific Investigations
Office of Compliance

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Acting Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations
Office of Compliance

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

/s/

Jean Mulinde
7/31/2008 11:19:34 AM
MEDICAL OFFICER

Tejashri Purohit-Sheth
7/31/2008 12:17:53 PM
MEDICAL OFFICER



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

Date: July 31, 2008

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

Through: Jodi Duckhorn, M.A., Team Leader
**Patient Labeling and Education Team
Division of Risk Management (DRISK)**

From: Sharon R. Mills, BSN, RN, CCRP
Patient Product Information Specialist
**Patient Labeling and Education Team
Division of Risk Management (DRISK)**

Subject: Memo to File Re: Review of Patient Labeling (Medication Guide)

Drug Name(s): Spiriva Respimat (tiotropium bromide inhalation spray)

Application Type/Number: NDA 21-936

Applicant/sponsor: Boehringer Ingelheim

OSE RCM #: 2007-2523

Boehringer Ingelheim submitted an original New Drug Application, NDA 21-936, for Spiriva Respimat (tiotropium bromide inhalation spray) on November 16, 2007. The proposed indication is for the long-term, once-daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.

Spiriva Handihaler (tiotropium bromide inhalation powder) is an approved product under NDA 21-395 and contains the same active ingredient. Spiriva Respimat (tiotropium bromide inhalation spray) represents a new dosage form.

The review division does not plan to address labeling during this review cycle; therefore, we defer our review of the Medication Guide until such time as the review division plans labeling discussions. Please send a new consult for review of the Medication Guide if and when labeling discussions are planned.

Please let us know if you have any questions.

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

/s/

Sharon Mills
7/31/2008 02:40:35 PM
DRUG SAFETY OFFICE REVIEWER

Jodi Duckhorn
7/31/2008 04:48:20 PM
DRUG SAFETY OFFICE REVIEWER



DEPARTMENT OF HEALTH AND HUMAN SERVICES

MEMORANDUM

Food and Drug Administration
Office of Device Evaluation
9200 Corporate Boulevard
Rockville, MD 20850

N21936 – Regulatory Consult

Date: June 1, 2008
To: The Record
From: Sugato De, Biomedical Engineer
Device: Spiriva Respimat Inhalation Spray

Office: HFZ-480
Division: DAGID/ARDB

I. Background

CDER has requested an evaluation of the Spiriva Respimat Device from a manufacturing and quality control perspective. From this specific perspective, there are no specific issues from the device standpoint that require further information. The primary concerns from the device perspective, assuming that adequate performance testing has been provided to demonstrate that the Respimat inhaler performs as specified, are in regards to human factors issues that may arise during the use of the device as a functional unit.

II. Device Description

The Spiriva Respimat Inhalation Spray consists of the Respimat inhaler and one cartridge containing Spiriva inhalation solution. The device is packaged as a functional unit containing two composite entities, the cartridge and the inhaler. The device has been developed for a one-time daily application. To administer one dose of medication and as typical for many metered dose inhalers, two actuations of the Respimat inhaler are applied. Spiriva Respimat Inhalation Spray will be used with only one cartridge, which is labeled for thirty doses. Once a cartridge is inserted into a Respimat inhaler, the drug product can be in use for up to three months. This is the maximum period of administration, including possible times of non-use.

The inhalation solution for Spiriva Respimat is a sterile aqueous formulation containing the active substance tiotropium bromide monohydrate and excipients. The recommended dosage is one dose comprising two actuations one time per day. Each dose from the Respimat inhaler delivers 5 µg of tiotropium in 22.1 µl of solution from the inhaler mouthpiece.

The cartridge contains the Spiriva inhalation solution that is filled into a (b) (4) plastic container, closed with a plastic snap-fit cap and tamper evident seal prior to being inserted and crimped into an aluminum cylinder. A detailed description of design and function of the cartridge is given in the submission. The cartridge is designed to be used specifically with the Respimat inhaler and is inserted into the inhaler by the patient prior to the initial use.

The Respimat inhaler is a hand held, pocket-sized oral inhalation device that uses mechanical energy to generate a slow moving aerosol cloud of medication from a metered volume of drug solution. It delivers the dosage form to the patient but is not stored in contact with the inhalation solution during long term storage.

The Respimat key principle is to meter a constant volume of inhalation and to nebulize it by forcing it through a very fine nozzle called the uniblock. As the uniblock has two fine outlets, two jets of solution are formed. They impinge on each other creating an aerosol cloud which is inhaled by the patient. The cartridge with the inhalation solution is connected to the Respimat inhaler by a capillary tube which has an integrated non-return valve in its upper end. The transparent base protects the cartridge during use and is connected to the case upper part. It can be removed for inserting the cartridge by pressing an integrated safety catch. For filling the inhaler metering chamber, the transparent base of the Respimat is rotated 180 degrees. This rotation is transformed into a downward movement, which compresses a spring and moves the capillary to a defined lower position. The downward movement under pressure is generated in the metering chamber. When the patient actuates the inhaler by pressing the dose release button, the mechanical power of the spring pushes the capillary upwards and closes the non-return valve, thus pressing the inhalation solution through the uniblock. Two jets are formed that impinge on each other to generate the aerosol.

III. Comments

Based on the documents provided for review, no specific concerns or issues were identified regarding the manufacturing and quality control for the device. However, it is recommended that further information be provided concerning how the cartridge for the inhalation solution interfaces with the subject inhaler. Specifically, as this device may be used in a home setting, it is recommended that relevant human factors testing be performed to verify that the user can adequately connect the cartridge to the inhaler and fill the cartridge with inhalation solution by following the instructions provided in the labeling. As the cartridge is labeled for thirty doses, usability studies should be performed that the device performs as specified for all thirty doses, and over the three months, the specified period of time over which the device should be used. Finally, if it has not already been provided, it is recommended that the sponsor provide validation testing for the physical tolerances of the cartridge container.

IV. Recommendation

It is recommended that the following concerns be addressed by the sponsor.

1. Please indicate whether the device component of your product has undergone any Human Factors studies to verify proper usage and to identify any risks associated with user error. If so, please provide results of the study, including information on protocols, pass/fail criteria, results and conclusions. Specifically, because your device may be used in a home setting, it is recommended that relevant human factors testing be performed to verify that the user can (1) adequately connect the cartridge to the inhaler and (2) fill the cartridge with inhalation solution by following the instructions provided in the labeling. If Human Factors studies were not performed, please give a detailed rationale for why such testing was deemed to be unnecessary. For more information regarding Human Factors, please visit <http://www.fda.gov/cdrh/humanfactors/>.
2. Please provide adequate usability studies to demonstrate that that the cartridge associated with the use of your device performs as specified for each of the thirty doses for which it is intended. In addition, it is recommended that simulated lifetime testing may be performed to demonstrate that the cartridge component remains functional over the three months, the indicated maximum period of time over which the device should be used.

**REGULATORY PROJECT MANAGER LABELING REVIEW
(PHYSICIAN LABELING RULE)**

Division of Pulmonary and Allergy Products

Application Number: NDA 21-936

Name of Drug: SPIRIVA RESPIMAT® (tiotropium bromide inhalation spray)

Applicant: Boehringer Ingelheim

Material Reviewed:

Submission Date(s): November 16, 2007

Receipt Date(s): November 16, 2007

Submission Date of Structure Product Labeling (SPL): November 16, 2007

Type of Labeling Reviewed: Word

Background and Summary

This review provides a list of revisions for the proposed labeling that should be conveyed to the applicant. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

Review

The following issues/deficiencies have been identified in your proposed labeling.

Highlights

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

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

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

2. Regarding Contraindications “theoretical” possibilities must not be listed (i.e., hypersensitivity to the drug). If the contraindication is not theoretical, then it must be worded to explain the type and nature of the adverse reaction. This also applies to the Contraindications Section of the FPI.
3. Refer to 21CFR 201.57 (a) (11) regarding what information to include under the Adverse Reactions heading in Highlights. Remember to list criteria used to determine inclusion (e.g. incidence rate).

Full Prescribing Information (FPI)

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

9. There is no requirement that the Patient Package Insert (PPI) or Medication Guide (MG) be a subsection under the Patient Counseling Information section. If the PPI or MG is reprinted at the end of the labeling, include it as a subsection. However, if the PPI or MG is attached (but intended to be detached) or is a separate document, it does not have to be a subsection, as long as the PPI or MG is referenced in the Patient Counseling Information section.
10. Any FDA-approved patient labeling must be appended to or accompany the labeling as a separate document (Note: This requirement is in effect as of June 30, 2007).

Recommendations

Boehringer Ingelheim should address the identified deficiencies/issues and re-submit labeling by April 16, 2008. This updated version of labeling will be used for further labeling discussions.

Miranda Raggio
Regulatory Project Manager

Supervisory Comment/Concurrence:

Sandy Barnes
Chief, Project Management Staff

Drafted: Miranda Raggio/January 10, 2008

Revised/Initialed:

Finalized:

Filename: CSO Labeling Review Template (updated 1-16-07).doc

CSO LABELING REVIEW OF PLR FORMAT

APPEARS THIS WAY ON ORIGINAL



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

/s/

Miranda Raggio
2/13/2008 02:23:33 PM
CSO

Miranda Raggio
2/13/2008 02:23:49 PM
CSO

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-936 Supplement # Efficacy Supplement Type SE-

Proprietary Name: SPIRIVA Respimat
Established Name: tiotropium bromide inhalation spray
Strengths: 5mg (2 inhalations of 2.5mcg each)

Applicant: Boehringer Ingelheim Pharmaceuticals, Inc.
Agent for Applicant (if applicable):

Date of Application: 11-16-07
Date of Receipt: 11-16-07
Date clock started after UN:
Date of Filing Meeting: 12-20-07
Filing Date: 1-15-08
Action Goal Date (optional): 9-2-08 User Fee Goal Date: 9-16-08

Indication(s) requested: long-term, once daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema

Type of Original NDA: (b)(1) (b)(2)
AND (if applicable)
Type of Supplement: (b)(1) (b)(2)

NOTE:

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S P
Resubmission after withdrawal? Resubmission after refuse to file?
Chemical Classification: (1,2,3 etc.)
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES NO

User Fee Status: Paid Exempt (orphan, government)
Waived (e.g., small business, public health)

NOTE: If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES NO
If yes, explain: NDA 21-395, Spiriva HandiHaler (tiotropium bromide).
Applicant is Boehringer Ingelheim

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES NO

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES NO
If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES NO

- Does the submission contain an accurate comprehensive index? YES NO
If no, explain:

- Was form 356h included with an authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES NO
If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES

2. This application is an eNDA or combined paper + eNDA YES

This application is: All electronic Combined paper + eNDA

This application is in: NDA format CTD format

Combined NDA and CTD formats

Does the eNDA, follow the guidance?
(<http://www.fda.gov/cder/guidance/2353fnl.pdf>) YES NO

If an eNDA, all forms and certifications must be in paper and require a signature.

If combined paper + eNDA, which parts of the application were submitted in electronic format? Most of the NDA is submitted electronically. An archival/review copy was sent in paper form, and includes the required forms with signatures**

Additional comments: **Module 3 documents submitted as paper with the SAD dataset for drug product primary stability data and the Quality Overall Summary(Module 2.3) submitted electronically.

3. This application is an eCTD NDA. YES
If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments: Hybrid

- Patent information submitted on form FDA 3542a? YES NO
- Exclusivity requested? YES, Three Years NO
NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

- Correctly worded Debarment Certification included with authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

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 . . ."

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included? YES NO
- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES NO
- Is this submission a partial or complete response to a pediatric Written Request? YES NO

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES NO
(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)

NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.

- Field Copy Certification (that it is a true copy of the CMC technical section) YES NO
- PDUFA and Action Goal dates correct in tracking system? YES NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: 46,687 and 65,127

- Are the trade, established/proper, and applicant names correct in COMIS? YES NO
If no, have the Document Room make the corrections.

- End-of-Phase 2 Meeting(s)? Date(s) _____ NO

If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s) Date(s) April 20, 2005 NO
If yes, distribute minutes before filing meeting.
- Any SPA agreements? Date(s) _____ NO
If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES NO
If no, request in 74-day letter.
- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
Was the PI submitted in PLR format? YES NO
If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:
- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES NO
- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES NO
- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
N/A YES NO
- Risk Management Plan consulted to OSE/IO? N/A YES NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA YES NO

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES NO
- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES NO
If no, did applicant submit a complete environmental assessment? YES NO

- | | | | | |
|---|-----|--------------------------|----|--------------------------|
| If EA submitted, consulted to EA officer, OPS? | YES | <input type="checkbox"/> | NO | <input type="checkbox"/> |
| • Establishment Evaluation Request (EER) submitted to DMPQ? | YES | <input type="checkbox"/> | NO | <input type="checkbox"/> |
| • If a parenteral product, consulted to Microbiology Team? | YES | <input type="checkbox"/> | NO | <input type="checkbox"/> |

ATTACHMENT

MEMO OF FILING MEETING

DATE: December 20, 2007

NDA #: 21-936

DRUG NAMES: SPIRIVA Respimat (tiotropium bromide inhalation spray)

APPLICANT: Boehringer Ingelheim

BACKGROUND:

(Provide a brief background of the drug, (e.g., molecular entity is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

ATTENDEES: Tim McGovern, Ruthi Davi, Qian Li, Wei Qiu, Alan Schroeder, Prasad Peri, Theresa Michele, Badrul A. Chowdhury, Ali Al-Hakim

ASSIGNED REVIEWERS (including those not present at filing meeting) :

<u>Discipline/Organization</u>	<u>Reviewer</u>
Medical:	Theresa Michele
Secondary Medical:	
Statistical:	Ruthianna Davi
Pharmacology:	Luqi Pei
Statistical Pharmacology:	
Chemistry:	Alan Schroeder
Environmental Assessment (if needed):	
Biopharmaceutical:	Sandra Suarez
Microbiology, sterility:	
Microbiology, clinical (for antimicrobial products only):	
DSI:	
OPS:	
Regulatory Project Management:	Miranda Raggio
Other Consults:	

Per reviewers, are all parts in English or English translation? YES NO

If no, explain:

CLINICAL FILE REFUSE TO FILE

• Clinical site audit(s) needed? YES NO
If no, explain:

• Advisory Committee Meeting needed? YES, date if known 6-11-08 NO

• 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? N/A YES NO

CLINICAL MICROBIOLOGY N/A FILE REFUSE TO FILE

STATISTICS	N/A <input type="checkbox"/>	FILE <input checked="" type="checkbox"/>	REFUSE TO FILE <input type="checkbox"/>
BIOPHARMACEUTICS		FILE <input checked="" type="checkbox"/>	REFUSE TO FILE <input type="checkbox"/>
	• Biopharm. study site audits(s) needed? YES		<input type="checkbox"/> NO <input checked="" type="checkbox"/>
PHARMACOLOGY/TOX	N/A <input type="checkbox"/>	FILE <input checked="" type="checkbox"/>	REFUSE TO FILE <input type="checkbox"/>
	• GLP audit needed?	YES <input type="checkbox"/>	NO <input type="checkbox"/>
CHEMISTRY		FILE <input checked="" type="checkbox"/>	REFUSE TO FILE <input type="checkbox"/>
	• Establishment(s) ready for inspection?	YES <input type="checkbox"/>	NO <input type="checkbox"/>
	• Sterile product?	YES <input type="checkbox"/>	NO <input type="checkbox"/>
	If yes, was microbiology consulted for validation of sterilization?	YES <input type="checkbox"/>	NO <input type="checkbox"/>

ELECTRONIC SUBMISSION:

Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:

(Refer to 21 CFR 314.101(d) for filing requirements.)

- The application is unsuitable for filing. Explain why:
- The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
- No filing issues have been identified.
- Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.
2. If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
3. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
4. If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)
5. Convey document filing issues/no filing issues to applicant by Day 74.

Appendix A to NDA Regulatory Filing Review

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the

original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

**Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES NO

If “No,” skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):
3. Is this application for a drug that is an “old” antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.) YES NO

If “Yes,” skip to question 7.

4. Is this application for a recombinant or biologically-derived product? YES NO

If “Yes “contact your ODE’s Office of Regulatory Policy representative.

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.
- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved? YES NO

(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

If “No,” to (a) skip to question 6. Otherwise, answer part (b and (c)).

- (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? YES NO

- (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES NO

If “Yes,” (c), list the pharmaceutical equivalent(s) and proceed to question 6.

If “No,” to (c) list the pharmaceutical equivalent and contact your ODE’s Office of Regulatory Policy representative.

Pharmaceutical equivalent(s):

6. (a) Is there a pharmaceutical alternative(s) already approved? YES NO

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

If “No,” to (a) skip to question 7. Otherwise, answer part (b and (c)).

- (b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES NO

- (c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES NO

If “Yes,” to (c), proceed to question 7.

NOTE: *If there is more than one pharmaceutical alternative approved, consult your ODE’s Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.*

If “No,” to (c), list the pharmaceutical alternative(s) and contact your ODE’s Office of Regulatory Policy representative. Proceed to question 7.

Pharmaceutical alternative(s):

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)? YES NO

If “No,” skip to question 8. Otherwise, answer part (b).

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12.

8. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsules to solution”).

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)).) YES NO

10. 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 less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9)). YES NO

11. Is the application for a duplicate of a listed drug whose only difference is YES NO

that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9).

12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? (This is different from the patent declaration submitted on form FDA 3542 and 3542a.) YES NO

13. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

- Not applicable (e.g., solely based on published literature. See question # 7)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):
- Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):
- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.

YES NO

If "Yes," what is the listed drug product(s) and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug

Was this listed drug product(s) referenced by the applicant? (see question # 2)

YES NO

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?

N/A YES NO

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES NO

If "Yes," please list:

Application No.	Product No.	Exclusivity Code	Exclusivity Expiration

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

/s/

Miranda Raggio
2/13/2008 02:19:16 PM
CSO

Miranda Raggio
2/13/2008 02:19:36 PM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

MEMORANDUM

Pre-Decisional Agency Information

Date: February 12, 2008

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

From: Michelle Safarik, PA-C – Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Subject: DDMAC labeling comments for Spiriva Respimat (tiotropium bromide inhalation spray)
NDA 21-936

DDMAC has reviewed the proposed product labeling (PI) and proposed carton and container labeling for Spiriva Respimat (tiotropium bromide inhalation spray) (Spiriva Respimat) submitted for consult on December 5, 2007.

We acknowledge that the proposed PI for Spiriva Respimat borrows heavily from that of the currently-approved Spiriva Handihaler PI (NDA 21-395); thus, DDMAC may be commenting on sections of the Spiriva Respimat label that contain already-approved language from the Spiriva Handihaler PI.

We offer the following comments.

Highlights

Dosage and Administration

1.  (b) (4)

For clarity, we recommend specifying that the dose is 2 puffs daily, and that 1 puff contains 2.5 mcg of drug.

Drug Interactions

 (b) (4)

According to the draft Guidance for Industry Labeling Human Prescription Drug and Biological Products – Implementing the New Content and Format Requirements (page 13), “In general, drugs that were found not to interact or to interact in a nonclinically relevant way should not be included under this heading, nor should details of drug interaction studies. However, it may be appropriate to include pertinent negative findings of drug interaction studies under this heading if the interaction would otherwise be anticipated or is of special concern (e.g., other drugs in the class need a dosage adjustment or if the drugs are commonly coadministered).” Please consider these directives when deciding whether or not to include the above statements.

Full Prescribing Information

Adverse Reactions

Clinical Trials Experience

[REDACTED] (b) (4)

[REDACTED] (b) (4) is promotional in tone, minimizes the risks of Spiriva Respimat therapy, and is not in the current Spiriva Handihaler PI. Therefore, we recommend deletion.

[REDACTED] (b) (4)

We recommend revising “[REDACTED]” (b) (4)

Less Common Adverse Reactions

[REDACTED] (b) (4)

While the same statement appears in the Adverse Reactions section of the current Spiriva Handihaler PI, should information from the Precautions-Geriatric Use section of the current Spiriva Handihaler PI providing specifics about the differences in incidences between drug and placebo also be included?

Drug Interactions

1. (Please see comment under Highlights-Drug Interactions.)

Use in Specific Populations

Geriatric Use

(b) (4)

(b) (4) is promotional in tone and minimizes the risks of Spiriva Respimat therapy; therefore, we recommend deletion. In addition, would it be possible to provide context (b) (4)“?

(b) (4)

Was this numerical difference statistically and/or clinically significant? If so, the sentence, (b) (4)

(b) (4) minimizes the risks of Spiriva Respimat therapy, and stronger language and/or placement in a different section of the proposed PI may be warranted.

Description

(b) (4)

“(b) (4) are extremely promotional in tone and have major promotion and advertising implications. Therefore, we strongly recommend deletion.

Clinical Pharmacology

Mechanism of Action

(b) (4)

Would it be possible to provide context (b) (4) ?

Pharmacokinetics

Distribution

(b) (4)

Would it be possible to provide context (b) (4) ”?

Clinical Studies

(b) (4)

We recommend consulting SEALD to determine if (b) (4) constitute substantial evidence to support such claims in labeling.

(b) (4)

Is the inclusion of these secondary endpoints primarily supportive of the primary endpoint? If so, we recommend including a sentence stating such. Or, are they supported by data considered substantial evidence to

include in labeling? If so, we recommend providing context for the results by including the data.

Patient Counseling Information

1. For consistency with the Warnings and Precautions section of the proposed PI, we recommend including information on paradoxical bronchospasm and coexisting conditions.

FDA-Approved Patient Labeling

1. We recommend consulting DSRCs for comments on formatting, ease of readability, and consistency.

[REDACTED] (b) (4)

[REDACTED] (b) (4) These terms have major promotional implications; therefore, we recommend deletion if they are not accurate. In addition, [REDACTED] (b) (4) is extremely promotional in tone and we recommend deletion (please see comment under “Description”). Moreover, without adequate evidence to demonstrate that [REDACTED] (b) (4) we strongly recommend deletion. Overall, these terms and phrases are not appropriate for Patient’s Instructions for Use.

Carton and Container Labeling

[REDACTED] (b) (4)

For consistency with the How Supplied/Storage and Handling section of the proposed PI, we recommend adding the phrase, “[o]r when the locking mechanism is engaged (60 actuations), whichever comes first.”

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

/s/

Michelle Safarik
2/12/2008 10:40:17 AM
DDMAC REVIEWER

DSI CONSULT: Request for Clinical Inspections

Date: January 10, 2007

To: Leslie Ball, M.D., Branch Chief, GCP2
Constance Lewin, M.D., M.P.H, Branch Chief, GCP1
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: Theresa Michele, Medical Reviewer, Division of Pulmonary and Allergy Products, HFD- 570
Charles Lee, Medical Team Leader, Division of Allergy and Pulmonary Products, HFD-570

From: Miranda Raggio, Regulatory Project Manager, Division of Pulmonary and Allergy Products, HFD-570

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA 21-936
Sponsor/Sponsor contact information (to include phone/email): Boehringer Ingelheim Pharmaceuticals, Inc., Jeff Snyder, Executive Director, Drug Regulatory Affairs, 203-778-7941
Drug: tiotropium bromide inhalation spray
NME: No
Standard or Priority: Standard
Study Population < 18 years of age: none (subjects 40 years or older with a diagnosis of COPD)
Pediatric exclusivity: No

PDUFA: September 16, 2008
Action Goal Date: September 2, 2008
Inspection Summary Goal Date: August 16, 2008

II. Background Information

New application or supplement? New application

Indication: long-term, once daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema COPD

Drug: tiotropium is a specific antagonist at muscarinic acetylcholine receptors (anticholinergic). A product containing the same drug substance, tiotropium bromide monohydrate, was previously approved for use as inhalation powder with the HANDIHALER inhalation device (dry powder inhaler), [NDA 21-395, approved January 30, 2004]. Tiotropium bromide inhalation spray will be

used with the RESPIMAT device, a hand-held, pocket-sized, multi-dose, oral inhalation device that generates a slow-moving aerosol cloud of medication from the aqueous solution.

Disease: Chronic obstructive pulmonary disease (COPD) is a chronic progressive disease caused by chronic inflammation and destruction of the airways and lung parenchyma, and is usually associated with tobacco smoking or prolonged exposure to other noxious particles and gasses. The disease is characterized by progressive airflow obstruction that is sometimes partially reversible with the administration of a bronchodilator. The typical symptoms are cough, excess sputum production, and dyspnea.

Pivotal studies: There were 4 clinical efficacy and safety studies considered by the applicant to be pivotal in their drug development program. These trials are grouped into two replicative protocols.

- 205.251 and 205.252: 12-week comparison of the safety and efficacy of tiotropium Respimat (5 mcg and 10 mcg) to ipatropium bromide (active comparator) and placebo in patients with COPD. The primary endpoint for these studies was trough FEV₁ at 12 weeks. Study 205.251 enrolled a total of 361 subjects and was conducted at 39 different centers in 4 ex-US countries (Germany, Italy, Switzerland, and South Africa). Study 205.252 enrolled a total of 358 subjects and was conducted at 25 different centers in the US and Canada.
- 205.254 and 205.255: 48 week comparison of the safety and efficacy of tiotropium Respimat (5 mcg and 10 mcg) to placebo in patients with COPD; additional vital status information on prematurely withdrawn patients is listed under protocol 205.392. The primary endpoint for these studies was trough FEV₁ at 48 weeks. In addition, combined data from these studies is being used to support a labeling claim that Spiriva Respimat decreases COPD exacerbations (frequency and time to first exacerbation). Study 205.254 enrolled 983 subjects and was conducted at 77 different centers in 14 countries (Europe and North America). Study 205.255 enrolled 1007 subjects and was conducted in 79 different centers in 15 countries (Europe, North American, Africa, and Australia).
- A mortality signal was observed in the 48-week studies in favor of placebo. This issue was discussed at an advisory board meeting of the Drug Safety Oversight Committee and also with the sponsor at a Type A meeting. It was determined in these meetings that no safety signal existed for Spiriva Handihaler (a marketed product) and additional follow up data should be gathered on patients with early discontinuations from the 205.254 and 205.255 trials to determine if differential discontinuation may have been a confounding factor. These follow up data are under protocol 205.392.

III. Protocol/Site Identification

- Study 205.252: A randomized, double-blind, double-dummy, placebo- and active-controlled, parallel group efficacy and safety comparison of 12-week treatment of two doses [5 µg (2 actuations of 2.5 µg) and 10 µg (2 actuations of 5 µg)] of tiotropium inhalation solution delivered by the Respimat inhaler, placebo and ipratropium bromide inhalation aerosol (MDI) in patients with chronic obstructive pulmonary disease (COPD)

- Study 205.254: A randomized, double-blind placebo controlled, parallel group efficacy and safety comparison of one-year treatment of two doses [5 µg (2 actuations of 2.5 µg) and 10 µg (2 actuations of 5 µg)] of tiotropium inhalation solution delivered by the Respimat inhaler, placebo and ipratropium bromide inhalation aerosol (MDI) in patients with chronic obstructive pulmonary disease (COPD)
- Study 205.255: A randomized, double-blind placebo controlled, parallel group efficacy and safety comparison of one-year treatment of two doses [5 µg (2 actuations of 2.5 µg) and 10 µg (2 actuations of 5 µg)] of tiotropium inhalation solution delivered by the Respimat inhaler, placebo and ipratropium bromide inhalation aerosol (MDI) in patients with chronic obstructive pulmonary disease (COPD)
- Study 205.392: A retrospective collection of vital status data and pulmonary medication history for patients with chronic obstructive pulmonary disease (COPD) who withdrew prematurely from either of two one-year trials (205.254, 205.255) of tiotropium solutions delivered by the Respimat inhaler

Site # (Name,Address, Phone number, email, fax#)	Protocol #	Number of Subjects	Indication
Eugene Shmelev, MD Site # 07402 City Clinical Hospital N11 6 Dvintsev Str 127018 Moscow, Russia +7 (0)95 465 52 64	205.254 and 205.392	48 subjects	COPD
K. Scott Miller, MD Sites # 12, and 01512 Lowcountry Lung and Critical Care PA 9150-B Medcom St. Charleston, SC 29406-7108 Phone: (843) 572-3330 Fax: (843) 572-1255	205.252, 205.255, and 205.392	27 subjects in 205.252 and 27 subjects in 205.255	COPD

IV. Site Selection/Rationale

DSI consult is being requested for the tiotropium Respimat NDA. Although tiotropium Respimat does not represent a new chemical entity, a complete stand-alone clinical program was completed in accordance with Divisional policy regarding new respiratory delivery systems. In addition, a potential mortality signal was identified in this program, requiring additional safety review. In choosing sites for audit, no outliers were identified with regard to financial disclosure, protocol violations, or site specific efficacy. Sites in Russia were notable for having all of the unexplained deaths in the study (safety signal). Sites were also chosen in order to maximize the number of pivotal studies audited utilizing the least travel resources.

1. Eugen Shmelev, MD (Site #07402, Study 205.254)
City Clinical Hospital N11
6 Dvintsev Str
127018 Moscow, Russia

This site was the second highest enroller for the pivotal 48 week Study 205.254, with 48 subjects. In addition, this site had the largest number of unexplained deaths in the study (4 deaths, 3 of which were unexplained). All deaths occurred in tiotropium Respimat groups.

2. K Scott Miller, MD (Site #12, Study 205.252; Site #01512, Study 205.255)
Lowcountry Lung and Critical Care PA
9150-B Medcom St.
Charleston, SC 29406-7108

This site was the high enroller for the pivotal 12 week Study 205.252, with 27 subjects. In addition, this site was also the highest US enroller for the pivotal 48 week Study 205.255, with 27 subjects.

Domestic Inspections:

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify): Participation in 2 of 4 pivotal studies

International Inspections:

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (specify) Largest number of unexplained deaths (safety signal)

V. Tables of Specific Data to be Verified (if applicable)

Should you require any additional information, please contact Miranda Raggio at Ph: 301-796-2109 or Theresa Michele at Ph: 301-796-1593.

Concurrence: (as needed)

Therese Michele/January 7, 2008 Medical Team Leader
Charles Lee/January 7, 2008 Medical Reviewer

Badrul Chowdhury/January 10, 2008 Director, Division Director (foreign inspection requests only)

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

/s/

Badrul Chowdhury
1/10/2008 04:23:46 PM