

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203108Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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

Date of This Memorandum: June 26, 2014
Requesting Office or Division: Division of Pulmonary, Allergy, and Rheumatology Products
Application Type and Number: NDA 203108
Product Name and Strength: Striverdi Respimat (Olodaterol) Inhalation Spray
2.5 mcg per actuation
Submission Date: June 2, 2014
Applicant/Sponsor Name: Boehringer Ingelheim
OSE RCM #: 2014-1186
DMEPA Primary Reviewer: Lissa C. Owens, PharmD
DMEPA Team Leader: Kendra Worthy, PharmD

1 PURPOSE OF MEMO

The Division of Pulmonary, Allergy, and Rheumatology Products requested that we review the revised container label, carton and insert labeling, and instructions for use (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.¹

2 CONCLUSIONS

The revised container label, carton and insert labeling, and instructions for use are acceptable from a medication error perspective.

¹ Owens, L. Label and Labeling Review for Striverdi Respimat (NDA 203108). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2013 January 10. 9 p. OSE RCM No.: 2012-1523.

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/s/

LISSA C OWENS
06/26/2014

KENDRA C WORTHY
06/26/2014

**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: June 23, 2014

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

Through: LaShawn Griffiths, RN, MSHS-PH, BSN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Melissa Hulett, MSN, MSBA, RN
Team Leader, Patient Labeling Team
Division of Medical Policy Programs (DMPP)

From: Twanda Scales, MSN/Ed., RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: Review of Patient Labeling: Medication Guide (MG) and
Instructions for Use (IFU)

Drug Name: STRIVERDI RESPIMAT (olodaterol)

Dosage Form and Route: Inhalation Spray

Application
Type/Number: NDA 203108

Applicant: Boehringer Ingelheim Pharmaceuticals, Inc.

1 INTRODUCTION

On May 14, 2012, Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI) submitted for the Agency's review a Class 1 Resubmission, New Drug Application (NDA 203108), for STRIVERDI RESPIMAT (olodaterol) Inhalation Spray. STRIVERDI RESPIMAT (olodaterol) inhalation spray is indicated for the long term, once daily-maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

A Complete Response action letter from the Agency was received by BIPI on March 14, 2013, referencing manufacturing quality issues that required resolution. At this time, BIPI is responding to all of the items addressed in the Complete Response action letter.

This review is written by the Division of Medical Policy Programs (DMPP) in response to a request by the Division of Pulmonary, Allergy and Rheumatology (DPARP) on June 19, 2014, for DMPP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for STRIVERDI RESPIMAT (olodaterol) inhalation spray.

2 MATERIAL REVIEWED

- Draft STRIVERDI RESPIMAT (olodaterol) inhalation spray, MG and Instructions for Use (IFU), received on June 2, 2014 and received by DMPP on June 19, 2014.
- Draft STRIVERDI RESPIMAT (olodaterol) inhalation spray Prescribing Information (PI) received on June 2, 2014 and received by DMPP June 19, 2014.
- Draft STRIVERDI RESPIMAT (olodaterol) inhalation spray comparator labeling, reviewed by DMPP on February 22, 2013.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG and IFU the target reading level is at or below an 8th grade level.

Additionally, 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 APHont to make medical information more

accessible for patients with vision loss. We have reformatted the MG and IFU documents using the Verdana font, size 11.

In our review of the MG and IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU are consistent with the prescribing information (PI)
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our annotated version of the MG and IFU are appended to this memo. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

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/s/

SHARON W WILLIAMS
06/23/2014

MELISSA I HULETT
06/23/2014

LASHAWN M GRIFFITHS
06/23/2014

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

PATIENT LABELING REVIEW

Date: February 22, 2013

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

Through: LaShawn Griffiths, RN, MSHS-PH, BSN
Associate Director, Patient Labeling Team
Division of Medical Policy Programs (DMPP)

Melissa Hulett, RN, BSN, MSBA
Team Leader, Patient Labeling Team
Division of Medical Policy Programs (DMPP)

From: Twanda Scales, RN, MSN/Ed.
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: DMPP Review of Patient Labeling Medication Guide (MG)

Drug Name: Olodaterol

Dosage Form and Route: Inhalation Spray

Application
Type/Number: NDA 203108

Applicant: Boehringer Ingelheim Pharmaceuticals, Inc.

1 INTRODUCTION

On May 14, 2012, Boehringer Ingelheim Pharmaceuticals, Inc. submitted a New Drug Application (NDA 203108) for Olodaterol Inhalation Spray. Olodaterol inhalation spray is indicated for the long term, once daily-maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. The conditionally approved proprietary name for Olodaterol is Striverdi Respimat.

On July 13, 2012, the Division of Pulmonary, Allergy and Rheumatology (DPARP) requested that the Division of Medical Policy and Programs (DMPP) review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for Olodaterol.

This review is written in response to a request by the Division of Division of Pulmonary, Allergy and Rheumatology (DPARP) for the Division of Medical Policy Programs (DMPP) to review the Applicant's proposed Medication Guide (MG) for Olodaterol Inhalation Spray.

2 MATERIAL REVIEWED

- Draft Olodaterol Inhalation Spray MG and Instructions for Use (IFU) received on March 14, 2012, and received by DMPP on February 13, 2013.
- Draft Olodaterol Inhalation Spray Prescribing Information (PI) received on March 14, 2012 and received by DMPP February 13, 2013.
- Approved Arcapta Neohaler (indacaterol maleate) comparator labeling dated September, 2012.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG and IFU the target reading level is at or below an 8th grade level.

Additionally, 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 APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG and IFU documents using the Verdana font, size 11.

In our review of the MG and IFU we have:

- simplified wording and clarified concepts where possible

- ensured that the MG and IFU are consistent with the prescribing information (PI)
- removed unnecessary or redundant information
- ensured that the MG and IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG and IFU are consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our annotated version of the MG and IFU are appended to this memo. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

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/s/

TWANDA D SCALES
02/22/2013

MELISSA I HULETT
02/22/2013

LASHAWN M GRIFFITHS
02/22/2013

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

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

Memorandum

Date: February 20, 2013

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

From: Matthew Falter, Regulatory Review Officer, Office of Prescription
Drug Promotion (OPDP), Division of Consumer Drug Promotion
(DCDP)

Roberta Szydlo, Regulatory Review Officer, OPDP, Division of
Professional Drug Promotion (DPDP)

CC: Lisa Hubbard, Acting Deputy Division Director, DPDP
Twyla Thompson, Group Leader, DCDP

Subject: NDA # 203108
OPDP labeling comments for STRIVERDI® RESPIMAT®
(olodaterol) Inhalation Spray (Striverdi Respimat)

OPDP has reviewed the proposed Package Insert (PI), Carton and Container Labeling, Medication Guide (MG), and Instructions for Use (IFU) for Striverdi Respimat submitted for consult on July 12, 2012.

OPDP's comments on the PI are based on the proposed draft marked-up labeling titled "FDA olo PI 2-13-13.doc" that was sent via email from DPARP to OPDP on February 13, 2013. OPDP's comments on the PI are provided directly in the marked-up document attached (see below).

OPDP's comments on the MG and IFU are based on the proposed draft marked-up labeling titled "striverdi MG 1-17-13.doc" that was sent via email from DPARP to OPDP on February 13, 2013. OPDP's comments on the MG and IFU are provided directly in the marked-up document attached (see below).

OPDP has reviewed the proposed carton and container labeling submitted by the applicant and available in the EDR at:

- <\\cdsesub1\EVSPROD\NDA203108\0017\m1\us\5585a.pdf>
- <\\cdsesub1\EVSPROD\NDA203108\0017\m1\us\5583a.pdf>
- <\\cdsesub1\EVSPROD\NDA203108\0017\m1\us\5584a.pdf>
- <\\cdsesub1\EVSPROD\NDA203108\0017\m1\us\ct5582a.pdf>
- <\\cdsesub1\EVSPROD\NDA203108\0028\m1\us\5708a.pdf>
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- <\\cdsesub1\EVSPROD\NDA203108\0028\m1\us\ct5705a.pdf>
- <\\cdsesub1\EVSPROD\NDA203108\0028\m1\us\5583a.pdf>
- <\\cdsesub1\EVSPROD\NDA203108\0028\m1\us\5584a.pdf>
- <\\cdsesub1\EVSPROD\NDA203108\0028\m1\us\5585a.pdf>
- <\\cdsesub1\EVSPROD\NDA203108\0028\m1\us\ct5582a.pdf>

We have no comments at this time on the proposed carton and container labeling.

Thank you for the opportunity to comment on the proposed labeling.

If you have any questions concerning the PI or carton and container labeling, please contact Roberta Szydlo at (301) 796-5389 or roberta.szydlo@fda.hhs.gov.

If you have any questions concerning the MG or IFU, please contact Matt Falter at (301) 796-2287 or matthew.falter@fda.hhs.gov.

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/s/

ROBERTA T SZYDLO
02/20/2013

MATTHEW J FALTER
02/20/2013



Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: February 14, 2013

From: CDER DCRP QT Interdisciplinary Review Team

Through: Norman Stockbridge, M.D., Ph.D.
Division Director
Division of Cardiovascular and Renal Products /CDER

To: Christine Chung, DPARP

Subject: QT-IRT Consult to NDA 203108

This memo responds to email correspondence from DPARP regarding questions from Boehringer Ingelheim about QT-related labeling language. The QT-IRT reviewed the following materials:

- IRT Review under IND 76362 (10/24/2008)
- IRT Review under NDA 203108 (02/11/2013)

QT-IRT Comments for DPARP

Our revised labeling recommendation is provided below. We defer final labeling decisions to the Division.

12.6 Cardiac Electrophysiology

The effect of STRIVERDI RESPIMAT on the QT/QTc interval of the ECG was investigated in 24 healthy male and female volunteers in a double-blind, randomized, placebo-and active (moxifloxacin) controlled study at single doses of 10, 20, 30, and 50 mcg. Dose dependent QTcI (individual subject corrected QT interval) prolongation was observed. The maximum mean (one-sided 95% upper confidence bound) difference in QTcI from placebo after baseline correction was 2.5 (5.6) ms, 6.1 (9.2) ms, (b) (4) ms and (b) (4) ms following doses of 10, 20, 30 and 50 mcg, respectively.

BACKGROUND

QT-IRT reviewed the results of a TQT study for olodaterol on 10/23/2008 and later commented on the Sponsor's proposed labeling language on 2/11/2013. In an email from the Sponsor to the

Project Manager dated 2/1/2013 the Sponsor noted that they were not able to duplicate the numbers provided by IRT. The IRT statistical reviewer re-evaluated the study results using the current statistical method. Although the maximum mean and one-sided 95% upper confidence bound numbers are different from the original assessment (10/23/2008), the ultimate conclusions remain the same. Revised labeling language was sent to the Sponsor.

A mixed model was used in the updated FDA analysis to obtain the point estimate and corresponding confidence intervals of $\Delta\Delta\text{QTcI}$ for each treatment group. Adjustment for multiple testing was not applied for all BI 1744 treatment groups. The model includes treatment, timepoints, gender, sequences, period, baseline QTcI and treatment by timepoints interaction as fixed effects. Each individual was defined as random effects. The results are displayed in Table 1.

Table 1. FDA Analysis: The Point Estimates and the 90% CIs for BI 1744 CL (10, 20, 30, and 50 mcg).

Treatment	Time	$\Delta\Delta\text{QTcI}$ (ms)	90% CI (ms)
BI 1744 CL 10 mcg	2 hrs	2.5	(-0.6, 5.6)
BI 1744 CL 20 mcg	40 min	6.1	(3.0, 9.2)
BI 1744 CL 30 mcg	40 min	7.6	(4.4, 10.8)
BI 1744 CL 50 mcg	40 min	8.7	(5.5, 11.8)

Thank you for requesting our input into the development of this product under NDA 203108. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cdcrpqt@fda.hhs.gov

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/s/

KEVIN M KRUDYS
02/14/2013

QIANYU DANG
02/14/2013

NORMAN L STOCKBRIDGE
02/14/2013

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

Application: NDA 203108
Application Type: Original NDA
Name of Drug: Olodaterol RESPIMAT Inhalation Spray
Applicant: Boehringer-Ingelheim
Submission Date: May 14, 2012
Receipt Date: May 14, 2012

Regulatory History and Applicant's Main Proposals

Boehringer-Ingelheim submitted a New Drug Application for olodaterol for long term, once daily bronchodilator treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema. The PI includes a Medication Guide and Patient Instructions for Use.

The submission also contains carton and container labeling.

Review of Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the 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).

In addition, the following labeling issues were identified:

In both the Highlights (HL) and Full Prescribing Information (FPI), applicant did not include the IFU; revise to state the following: **"See FDA-approved patient labeling (Medication Guide and Instructions for Use)"**

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 was conveyed to the applicant in the 74-day letter. The applicant was asked to correct these deficiencies and resubmit the PI in Word format by August 17, 2012. The resubmitted PI will be used for further labeling review.

RPM PLR Format Review of the Prescribing Information

Appendix

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

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

Comment:

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page 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 RPMs)**

- *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” in the drop-down menu 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 (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

- YES** 4. White space must be present before each major heading in HL.

Comment:

- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is

Selected Requirements of Prescribing Information (SRPI)

the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

YES

6. Section headings are presented in the following order in HL:

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

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES

7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES

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

Comment:

Highlights Limitation Statement

YES

9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

Comment:

Product Title

YES

10. Product title in HL must be **bolded**.

Comment:

Initial U.S. Approval

YES

Selected Requirements of Prescribing Information (SRPI)

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

Comment: *This is an NME. Applicant has left space holder for completion.*

Boxed Warning

YES

12. All text must be **bolded**.

Comment:

YES

13. Must have a centered 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**”).

Comment:

YES

14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” centered immediately beneath the heading.

Comment:

YES

15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

Comment:

YES

16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

N/A

17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

N/A

18. Must be listed in the same order in HL as they appear in FPI.

Comment:

N/A

19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(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, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

Comment:

N/A

20. 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

YES

Selected Requirements of Prescribing Information (SRPI)

21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)].”

Comment:

Dosage Forms and Strengths

- YES** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

- N/A** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

- YES** 25. 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

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

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: In the Highlights section for the Patient counseling information statement, include reference to the Instructions for Use (IFU) to state the following, “See 17 for PATIENT COUNSELING INFORMATION, Medication Guide, and Instructions for Use.”

Revision Date

- YES** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

Selected Requirements of Prescribing Information (SRPI)

GENERAL FORMAT

- NO** 28. A horizontal line must separate TOC from the FPI.
Comment:
- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: **“FULL PRESCRIBING INFORMATION: CONTENTS”**.
Comment:
- YES** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.
Comment:
- YES** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.
Comment:
- YES** 32. All section headings must be **bolded** and in UPPER CASE.
Comment:
- YES** 33. All subsection headings must be indented, not bolded, and in title case.
Comment:
- YES** 34. When a section or subsection is omitted, the numbering does not change.
Comment:
- YES** 35. 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:
-

Full Prescribing Information (FPI)

GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: **“FULL PRESCRIBING INFORMATION”**.
Comment:
- YES** 37. All section and subsection headings and numbers must be **bolded**.
Comment:
- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS

Selected Requirements of Prescribing Information (SRPI)

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** 39. 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 patient labeling must appear at the end of the PI upon approval.

Comment:

- YES** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment:

- N/A** 41. 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

Boxed Warning

- YES** 42. All text is **bolded**.

Comment:

- YES** 43. 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**”).

Selected Requirements of Prescribing Information (SRPI)

Comment:

- YES** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

- N/A** 45. If no Contraindications are known, this section must state “None”.

Comment:

Adverse Reactions

- YES** 46. When clinical trials adverse reactions data is 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 clinical practice.”

Comment:

- YES** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

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

Comment:

Patient Counseling Information

- YES** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- “See FDA-approved patient labeling (Medication Guide)”
 - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information)”
 - “See FDA-approved patient labeling (Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”
 - **Comment: Applicant did not include IFU; revise to “See FDA-approved patient labeling (Medication Guide and Instructions for Use).”**
-

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

/s/

CHRISTINE H CHUNG
02/01/2013

SANDRA L BARNES
02/01/2013

RPM FILING REVIEW

(Including Memo of Filing Meeting)

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

Application Information		
NDA # 203108 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Striverdi Established/Proper Name: olodaterol Respimat Dosage Form: Inhalation Spray Strengths: 2.5 mcg olodaterol per actuation		
Applicant: Boehringer-Ingelheim Agent for Applicant (if applicable):		
Date of Application: May 14, 2012 Date of Receipt: May 14, 2012 Date clock started after UN:		
PDUFA Goal Date: March 14, 2013		Action Goal Date (if different):
Filing Date: July 13, 2012		Date of Filing Meeting: June 26, 2012
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1 (new molecular entity)		
Proposed indication(s): Long-term, once-daily maintenance bronchodilator treatment of air flow obstruction in patients with COPD, including chronic bronchitis/emphysema		
Type of Original NDA: NME AND (if applicable) Type of NDA Supplement:		<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		<input type="checkbox"/> Convenience kit/Co-package <input checked="" type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (<i>if OTC product</i>):				
List referenced IND Number(s): IND 76362				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	✓			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	✓			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	✓			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		✓		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	✓			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>																				
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>																				
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i></p>																				
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? Check the <i>Electronic Orange Book</i> at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1451 1349 1587"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i> http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm</p>		<p>✓</p>																		

<p>If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>				
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested: did not specify, 5 years for NME</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>	✓			5 years NME
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>		✓		
<p>If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>				

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>				
Overall Format/Content	YES	NO	NA	Comment
<p>If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).</p>	✓			
<p>Index: Does the submission contain an accurate comprehensive index?</p>	✓			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p>	✓			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?				
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	✓			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	✓			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	✓			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	✓			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	✓			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature?	✓			

<p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>				
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			✓	All electronic

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			✓	

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	✓			
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>	✓			

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

If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>			✓	
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>	✓			
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>		✓		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	✓			
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	✓			
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input checked="" type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	✓			
Is the PI submitted in PLR format? ⁴	✓			

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

⁴ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	✓			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	✓			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	✓			
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	✓			QT-IRT has already reviewed pertinent study
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s) Date(s): 7/17/2008 Clinical & CMC separately <i>If yes, distribute minutes before filing meeting</i>	✓			

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 9/28/11 meeting preliminary comments only <i>If yes, distribute minutes before filing meeting</i>	✓			
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>			✓	

ATTACHMENT

MEMO OF FILING MEETING

DATE: June 26, 2012

BLA/NDA/Supp #: NDA 203108

PROPRIETARY NAME: (b) (4) Respimat

ESTABLISHED/PROPER NAME: olodaterol Respimat

DOSAGE FORM/STRENGTH: Inhalation Spray 2.5 mcg olodaterol per actuation

APPLICANT: Boehringer-Ingelheim

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Long-term, once-daily maintenance bronchodilator treatment of air flow obstruction in patients with COPD, including chronic bronchitis/emphysema

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Christine Chung	Y
	CPMS/TL:	Sandy Barnes	N
Cross-Discipline Team Leader (CDTL)	Theresa Michele		Y
Clinical	Reviewer:	Robert Lim	Y
	TL:	Theresa Michele	Y
Social Scientist Review (for OTC products)	Reviewer:		
	TL:		
OTC Labeling Review (for OTC products)	Reviewer:		
	TL:		
Clinical Microbiology (for antimicrobial products)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Elizabeth Shang Satjit Brar	Y
	TL:	Suresh Doddapaneni	Y
Biostatistics	Reviewer:	Robert Abugov	Y
	TL:	Joan Buenconsejo Tom Permutt	N Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Carol Rivera-Lopez	Y
	TL:	Molly Shea	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Craig Bertha	N
	TL:	Alan Schroeder	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Lissa Owens	Y
	TL:	Lubna Merchant	N
OSE/DRISK (REMS)	Reviewer:	Kendra Worthy	Y
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	Anthony Orenca	Y
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers			
Other attendees	Sally Seymour Nichelle Rashid Teena Thomas Ann Corken Dipti Kalfa Margie Goulding Janet Maynard, Susette Peng		

FILING MEETING DISCUSSION:

GENERAL	
<ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable
CLINICAL	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p>	<input checked="" type="checkbox"/> YES Date if known: 1/29/13 <input type="checkbox"/> NO <input type="checkbox"/> To be determined

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

Comments:	<input type="checkbox"/> Review issues for 74-day letter
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<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input checked="" type="checkbox"/> Review issues for 74-day letter</p>
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments: From CMC filing review “To be reviewed by Dr. Bertha, Senior CMC Reviewer”</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments: “entered by the ONDQA PM on 6/21/12”</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>

<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> FILE</p> <p><input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>CMC Labeling Review</u></p> <p>Comments:</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>REGULATORY PROJECT MANAGEMENT</p>	
<p>Signatory Authority: Curtis Rosebraugh, MD, MPH</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p> <p>Comments:</p>	
<p>REGULATORY CONCLUSIONS/DEFICIENCIES</p>	
<p><input type="checkbox"/></p>	<p>The application is unsuitable for filing. Explain why:</p>
<p><input checked="" type="checkbox"/></p>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p><input checked="" type="checkbox"/> Standard Review</p> <p><input type="checkbox"/> Priority Review</p>
<p>ACTIONS ITEMS</p>	
<p><input type="checkbox"/></p>	<p>Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).</p>
<p><input type="checkbox"/></p>	<p>If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).</p>
<p><input type="checkbox"/></p>	<p>If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.</p>

<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

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 OND ADRA or OND IO.

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/s/

CHRISTINE H CHUNG
02/01/2013

SANDRA L BARNES
02/01/2013

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: January 18, 2013

TO: Christine H. Chung, Regulatory Project Manager
Theresa M. Michele, M.D., M.P.H., Medical Officer-Team Leader
Robert Lim, M.D., Medical Officer
Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

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

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

Susan D. Thompson, M.D.
Acting Branch Chief, GCP Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 203108

APPLICANT: Boehringer-Ingelheim

DRUG: olodaterol

NME: Yes

THERAPEUTIC CLASSIFICATION/REVIEW: standard review

INDICATION: chronic obstructive pulmonary disease (COPD)

CONSULTATION REQUEST DATE: July 20, 2012 (signed)
INSPECTION SUMMARY GOAL DATE: January 9, 2013 (original)
January 18, 2013 (extension)

DIVISION ACTION GOAL DATE: February 21, 2013
PDUFA DATE: March 14, 2013

I. BACKGROUND:

Olodaterol, a long acting beta-agonist (LABA), is a selective agonist of the human beta₂-adrenoceptor and has reported low activity at the beta₁-adrenoceptor. This NME drug product is expected to have similar safety issues, such as cardiovascular adverse effects, as other products in this class including salmeterol, formoterol, and indacaterol, for the treatment of chronic obstructive pulmonary disease (COPD). The approved medical delivery device, Respimat[®], is a hand-held, multi-dose, oral inhalation device that generates a slow moving cloud of aerosolized medication from an aqueous solution.

Three adequate and well-controlled clinical studies were submitted in support of the applicant's NDA that were subject of these site inspections. As part of the clinical site audit, the CDER review division selected three domestic clinical sites and a single foreign site in Buenos Aires, Argentina for inspection, primarily based on the large number of randomized patients in the four 48-week pivotal trials.

Study 1222.13

Study 1222.13 was a randomized, double-blind, double-dummy, placebo-controlled, parallel group clinical trial that was used to support the sponsor's European clinical trial registration. The primary objective of this study was to assess the long-term efficacy and safety of once daily treatment of BI 1744 CL inhalation solution (5 µg [2 actuations of 2.5 µg] and 10 µg [2 actuations of 5 µg]) delivered via the Respimat[®] inhaler in patients with COPD.

The test product was BI 1744 CL oral inhalation solution - Respimat[®], administered at a dose of 5 µg and 10 µg once daily. The reference oral inhalation therapy or active comparator arm was Foradil[®] - Aerolizer[®] administered at a dose of 12 µg twice daily. There were two corresponding placebo oral inhalation treatment arms: (1) placebo inhalation solution - Respimat[®], and (2) placebo inhalation matching Foradil[®] - Aerolizer[®]. Two co-primary efficacy outcomes of the study, FEV₁ AUC 0-3 hour response and trough FEV₁ response at week 24 or day 169 are of specific interest to the review division, DPARP.

Study 1222.11

Study 1222.11 was a randomized, double-blind, placebo-controlled, parallel group clinical trial that was used to support the NDA 203108 submission. The primary objective of this study was to assess the long-term efficacy and safety of once daily treatment of BI 1744 CL inhalation solution (5 µg [2 actuations of 2.5 µg] and 10 µg [2 actuations of 5 µg]) delivered via the Respimat[®] inhaler in patients with COPD.

The test product was BI 1744 CL oral inhalation solution - Respimat[®], administered at a dose of 5 µg and 10 µg once daily. The reference oral inhalation therapy or comparator arm administered for 48 weeks treatment duration was placebo inhalation solution - Respimat[®]. The two co-primary efficacy outcomes of the study, FEV₁ AUC 0-3 hour

response and trough FEV1 response at week 12 (Day 85), are of specific interest to the review division, DPARP.

Study 1222.12

The study design, objectives, and primary endpoints for this study used to support the sponsor's NDA 203108 submission, were similar to Study 1222.11.

II. RESULTS:

Name of CI City, State	Protocol/Study Site	Insp. Date	Final Classification*
Maria Cristina De Salvo, MD Buenos Aires, Argentina	Protocol 1222.13 Site #2401 n=119 subjects enrolled	September 10-18, 2012	Preliminary: VAI
Philip A. Snell, M.D. Greer, SC	Protocol 1222.11 Site #1119 13 subjects enrolled	November 15-26, 2012	NAI
Thomas D. Kaelin, Jr., D.O. Charleston, SC	Protocol 1222.11 Site #1112 19 enrolled	August 27-30, 2012	NAI
Leonard J. Dunn, M.D. Clearwater, FL	Protocol 1222.12 Site #1207 61 subjects enrolled	August 22-31, 2012	NAI
Boehringer-Ingelheim Raritan, NJ	Sponsor	November 26 to December 3, 2012	Preliminary: NAI

*Key to Classifications

NAI = No deviation from regulations. Data acceptable.

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

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

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

CLINICAL STUDY SITE INVESTIGATORS

- 1. Maria Cristina De Salvo, M.D./Protocol 1222.13 Site #13 PI**
Buenos Aires, Argentina

a. What was inspected:

The inspection was conducted in accordance with Compliance Program 7348.811, from September 10 to 18, 2012. A total of 128 subjects were screened and 119 subjects were enrolled, and randomized. Ten patients discontinued and 109 subjects completed the study.

An audit of 20 subjects' records was conducted. The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

b. General observations/commentary:

Source documents for randomized subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the primary study endpoint were verifiable at the study site. There were no limitations during conduct of the clinical site inspection by ORA staff. There was no under-reporting of serious adverse events (SAEs) at this clinical study site.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. However, a Form FDA 483 (List of Inspectional Observations) was issued at the end of the inspection for not conducting the study according to investigational plan and not maintaining adequate investigational drug final disposition records.

Specifically:

(i) Patients #11947, #12079, #12104, #11935, #12052, #11931, and #12105 received an investigational treatment box(es) outside of that assigned by the Interactive Voice Response System (IVRS) for at least one visit from Visit #2-Visit #9.

(ii) The clinical study site did not maintain adequate investigational drug final disposition records and inventory at the study site. The study monitor could not locate some of the study medications returned by the following study patients: Subject #11947, #10950, #10871, #11931, #11932, and #12053.

OSI Medical Officer's Comments:

The List of Inspectional Observations was communicated to the DPARP Medical Team. Exhibits collected at the time of inspection along with Dr. De Salvo's October 5, 2012 response, provide documentation showing Subjects #11947, #12052, and #12105 received the correct investigational drug kits allocated through the IVRS system.

Four of the seven subjects (Subject #s 12079, 12104, 11935, and 11931) reported to have received study medication not assigned by the IVRS were dispensed the wrong box of study medication (30 day supply) on at least one visit and could have received a study medication that they were not randomized to (i.e. olodaterol, Foradil[®], or placebo). Since the ORA audit included review of only 20 subject records, it is not known whether similar errors occurred in the other 99 enrolled subjects. The review division, DPARP

Medical Team was made aware of the findings. The DPARP Medical Team conducted a sensitivity analysis excluding Dr. de Salvo's site, and mentioned to OSI that the on-going analysis has not changed their review decisions.

Although there were errors in study medication dispensation, it appears that the observed regulatory deficiencies were random and sporadic and only affected one of several study medication boxes received by a subject over the course of the study. These regulatory violations are unlikely to have a critical impact on data reliability for this NDA.

c. Assessment of data integrity:

Notwithstanding the issues noted above, data submitted by this clinical site appear acceptable for this specific indication.

Note: Observations noted above are based on preliminary communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

2. Philip Snell, M.D./Protocol 1222.11 Site #1119

Greer, S.C.

a. What was inspected:

The inspection was conducted in accordance with Compliance Program 7348.811, from August 27 to 31, 2012. A total of 20 subjects were screened and 13 subjects were enrolled. Eleven subjects completed the study.

An audit of the 13 enrolled subjects' records was conducted. The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

b. General observations/commentary:

Source documents for randomized subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the primary study endpoint were verifiable at the study site. There were no limitations during conduct of the clinical site inspection by ORA staff. There was no under-reporting of serious adverse events at this clinical study site.

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

c. Assessment of data integrity:

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

3. Thomas Kaelin, D.O./ Protocol 1222.11 Site #1112
Charleston, SC

a. What was inspected:

The inspection was conducted in accordance with Compliance Program 7348.811, from August 27 to 30, 2012. A total of 37 subjects were screened and 19 subjects were enrolled.

An audit of 12 randomized subjects' records was conducted. The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

b. General observations/commentary:

Source documents for randomized subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the primary study endpoint were verifiable at the study site. There were no limitations during conduct of the clinical site inspection by ORA staff. There was no under-reporting of serious adverse events at this clinical study site.

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

c. Assessment of data integrity:

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

4. Leonard J Dunn, M.D./Protocol 1222.12 Site #1207
Clearwater, FL

a. What was inspected:

The inspection was conducted in accordance with Compliance Program 7348.811, from August 22 to 31, 2012. A total of 78 subjects were screened and 61 subjects were enrolled. Thirty nine subjects completed the study.

Records of 13 of the 39 subjects who completed the study were audited. The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence with the IRB. Informed consent documents and sponsor-generated correspondence were also inspected.

b. General observations/commentary:

Source documents for randomized subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the primary study endpoint were verifiable at the study site. There were no limitations during conduct of the clinical site inspection by ORA staff. There was no under-reporting of serious adverse events (SAEs). Three subjects (Subject #6512, #6514 and #7038) were reported to have SAEs and no deaths occurred at this clinical study site.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (List of Inspectional Observations) was not issued at the end of the inspection. However, the following item was discussed at the clinical site close-out meeting. Specifically, Subject #6075 was documented as meeting both inclusion and exclusion criteria on February 17, 2009, and was randomized on the same date before study blood chemistry and hematology records (available on February 18, 2009) were signed off by the Principal Investigator on February 25, 2009, to verify that this subject met inclusion criteria for randomization.

c. Assessment of data integrity:

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

Note: Observations noted above are based on preliminary communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

SPONSOR

5. Boehringer Ingelheim (BI)

Raritan, NJ

a. What was inspected:

The inspection was conducted in accordance with Compliance Program 7348.810, from November 26 to December 3, 2012.

The inspection evaluated the following: documents related to study monitoring visits and correspondence, Institutional Review Board (IRB) approvals, completed Form FDA 1572s, monitoring reports, drug accountability, and training of staff and site monitors.

b. General observations/commentary:

The Sponsor maintained adequate oversight of the clinical trial. Monitoring of clinical investigator sites appeared to be adequate. The Sponsor took appropriate steps to bring noncompliant sites into compliance. At the conclusion of the inspection, no List of Inspectional Observations (Form FDA 483) was issued.

c. Assessment of data integrity:

The study appears to have been conducted adequately. Data submitted by this Sponsor appear acceptable in support of the respective indication.

Note: Observations noted above are based on preliminary communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

For this NDA, two U.S. clinical investigator sites for Protocol 1222.11, a single U.S. clinical investigator site for Protocol 1222.12, a single foreign clinical investigator site for Protocol 1222.13, and the Sponsor were inspected in support of this application.

No regulatory deficiencies were observed for Philip Snell, M.D. (Protocol 1222.11 Site #1119), Thomas Kaelin, D.O. (Protocol 1222.11 Site #1112), Leonard J. Dunn, MD (Protocol 1222.12 Site #1207), and the Sponsor. Regulatory deficiencies were observed for Maria Cristina De Salvo (Protocol 1222.13 Site #2401) related to not conducting the study according to the protocol and incomplete record keeping.

Based on review of inspectional findings for these clinical investigator and Sponsor sites, the study data collected appear generally reliable in support of the requested indication.

Note: Observations noted above are based on the preliminary communications from the field investigators; an inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the final EIRs.

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Anthony Orenca, M.D.
Medical Officer
Good Clinical Practice Assessment Branch
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/s/

ANTHONY J ORENCIA
01/18/2013

JANICE K POHLMAN
01/18/2013

SUSAN D THOMPSON
01/18/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling, and Packaging Review Memo

Date: January 18, 2013

Reviewer(s): Lissa C. Owens, PharmD
Division of Medication Error Prevention & Analysis

Team Leader: Lubna Merchant, M.S., PharmD
Division of Medication Error Prevention & Analysis

Drug Name(s) and Strength(s): Striverdi Respimat (Olodaterol) Inhalation Spray
2.5 mcg per actuation

Application Type/Number: NDA 203108

Applicant/sponsor: Boehringer Ingelheim Pharmaceuticals, Inc.

OSE RCM #: 2012-1523

*** This document contains proprietary and confidential information that should not be released to the public.***

Contents

1	Introduction.....	3
2	Methods and Materials Reviewed.....	3
3	Conclusions and Recommendations	3
	References.....	4
	Appendix.....	5

1 INTRODUCTION

This review evaluates the revised Striverdi Respimat container labels and carton labeling submitted by the Applicant in response to the Division of Medication Error Prevention and Analysis's (DMEPA's) previous comments in OSE Review #2012-1523, dated January, 10, 2013.

2 METHODS AND MATERIALS REVIEWED

The revised labels submitted to the FDA on January 17, 2013 (See Appendices A-C) and OSE Review #2012-1593, dated January 10, 2013, were evaluated to assess whether the revisions adequately address our concerns from a medication error perspective.

3 CONCLUSIONS AND RECOMMENDATIONS

The revised labels addressed all of DMEPA's concerns and we have no additional comments.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact OSE Regulatory Project Manager, Nichelle Rashid, at 301-796-3904.

REFERENCES

1. OSE Review #2012-1593, Label, Labeling, and Packaging Review for Striverdi Respimat, January 10, 2013, Owens, L.

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

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/s/

LISSA C OWENS
01/18/2013

LUBNA A MERCHANT
01/18/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling and Packaging Review

Date: January 10, 2013

Reviewer(s): Lissa Owens, PharmD
Division of Medication of Error Prevention and Analysis

Team Leader: Lubna Merchant, M.S., PharmD
Division of Medication of Error Prevention and Analysis

Division Director: Carol Holquist, RPh
Division of Medication of Error Prevention and Analysis

Drug Name(s) and Strength(s): Striverdi Respimat (Olodaterol) Inhalation Spray
2.5 mcg per actuation

Application Type/Number: NDA 203108

Applicant/sponsor: Boehringer Ingelheim Pharmaceuticals, Inc.

OSE RCM #: 2012-1523

*** This document contains proprietary and confidential information that should not be released to the public.***

Contents

1	Introduction.....	1
1.1	Product Information	1
2	Methods and Materials Reviewed.....	1
2.1	Selection of Medication Error Cases.....	1
2.2	Labels and Labeling	2
3	Integrated Summary of Medication Error Risk Assessment	2
4	Conclusions and Recommendations	2
	Appendices.....	4

1 INTRODUCTION

This review evaluates the proposed container label, carton and insert labeling and patient instructions for use for Striverdi Respimat (Olodaterol) Inhalation Spray NDA 203108 for areas of vulnerability that could lead to medication errors.

1.1 PRODUCT INFORMATION

The following product information is provided in the June 29, 2012 proprietary name submission:

- Active Ingredient: Olodaterol
- Indication of Use: Maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema
- Route of Administration: Oral Inhalation
- Dosage Form: Inhalation Spray
- Strength: 2.5 mcg per actuation
- Dose and Frequency: 2 actuations by mouth once daily
- How Supplied: Provided in a box containing the Respimat inhaler and the Respimat cartridge
- Storage: Room temperature; Protect from freezing

2 METHODS AND MATERIALS REVIEWED

The Division of Medication Error Prevention and Analysis (DMEPA) searched the FDA Adverse Event Reporting System (FAERS) database for any medication error reports. We also reviewed the labels and package insert labeling submitted by the Applicant for this product.

2.1 SELECTION OF MEDICATION ERROR CASES

Since the Respimat device is currently marketed (Combivent Respimat), we searched the FDA Adverse Event Reporting System (FAERS) database using the strategy listed in Table 1 to see if there are any device issues.

Table 1: FAERS Search Strategy	
Date	October 23, 2012
Drug Names	(Combivent Respima%) (Combivent Respima%)
MedDRA Search Strategy	Medication Errors (HLGT) Product Packaging Issues HLT Product Label Issues HLT Product Quality Issues (NEC) HLT

There were no reports retrieved from this search.

2.2 LABELS AND LABELING

Using the principals of human factors and Failure Mode and Effects Analysis,¹ along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted November 5, 2012 (Appendix A)
- Carton Labeling submitted November 5, 2012 (Appendix B)
- Professional Sample Label and Labeling submitted November 5, 2012 (Appendix C)
- Insert Labeling submitted November 5, 2012 (no image)
- Patient Instructions for Use November 5, 2012 (no image)

3 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESMENT

Although Olodaterol is a new molecular entity, we note that the Respimat device is currently marketed with the approved product, Combivent Respimat. The Respimat device proposed with this product is identical to the marketed device, and utilizes an identical PIFU. The device is co-packaged with the drug product and not available alone. Since the patient population and proposed device is the same as what is currently marketed, there should be minimal risk of use related errors. However, areas of the labels and labeling can be improved upon. We provide recommendations in the following section.

4 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

A. All Labels and Labeling

Although the established name is ½ the size of the proprietary name, it lacks prominence. Revise the established name so that it has a prominence commensurate to that of the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features per 21 CFR 201.10(g)(2).

B. All Container Labels

Relocate the company logo so that it appears at the bottom of the label.

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

C. Professional Sample Label and Labeling

Revise the color of the statement 'Professional Sample: Not For Sale' from [REDACTED] (b) (4) to improve readability.

D. Patient Instructions for Use

Remove the reference to the name [REDACTED] (b) (4) and update it to reflect the current proposed proprietary name when approved.

If you have further questions or need clarifications, please contact Nichelle Rashid, project manager, at 301-796-3904

4 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

LISSA C OWENS
01/10/2013

LUBNA A MERCHANT
01/10/2013

CAROL A HOLQUIST
01/10/2013



Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: October 21, 2012

From: CDER DCRP QT Interdisciplinary Review Team

Through: Norman Stockbridge, M.D., Ph.D.
Division Director
Division of Cardiovascular and Renal Products /CDER

To: Christine Chung, DPARP

Subject: QT-IRT Consult to NDA 203108

This memo responds to your consult to us dated May 14, 2012 regarding the Sponsor's proposed labeling. The QT-IRT received and reviewed the following materials:

- Your consult
- Proposed label

QT-IRT Comments for DPARP

QT-IRT previously reviewed the thorough QT study for olodaterol under IND (b)(4) and concluded that QT prolongation was observed at doses greater than 10 µg. The Sponsor's proposed language in section 12.2 of the label for this NDA appears to (b)(4)

(b)(4) T-IRT reports the **largest** time-matched mean difference over the collection period, as per ICH E14 guidance. QT-IRT recommends including the largest time-matched mean difference in the label.

Pre-dose QTc measurements in Phase 3 parallel group studies at weeks 6, 12, 24 and 48 are not suggestive of a delayed effect at the therapeutic dose.

The Sponsor's proposed language, followed by QT-IRT's recommended language is provided below.

Sponsor's Proposed Label

Electrophysiology

QT-IRT Proposed Label

QT-IRT recommends the following label language. We defer final decisions regarding labeling to the review division.

12.6 Cardiac Electrophysiology

The effect of (b) (4) RESPIMAT on the QT/QTc interval of the ECG was investigated in 24 healthy male and female volunteers in a double-blind, randomized, placebo- and active (moxifloxacin) controlled study at single doses of 10, 20, 30, and 50 mcg. Dose-dependent QTcF prolongation was observed. The maximum mean (95% upper confidence bound) difference in QTcF from placebo after baseline correction was (b) (4) ms following doses of 10, 20, 30 and 50 mcg, respectively.

Thank you for requesting our input into the development of this product under NDA 203108. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cdcrpqt@fda.hhs.gov

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/s/

KEVIN M KRUDYS
10/22/2012

MONICA L FISZMAN
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