

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
021747Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 21747	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Combivent Respimat Established/Proper Name: Ipratropium bromide/albuterol sulfate Dosage Form: Inhalation Spray Strengths: 100mcg/20mcg		
Applicant: Boehringer Ingelheim		
Date of Receipt: April 07, 2011		
PDUFA Goal Date: October 07, 2011		Action Goal Date (if different):
Proposed Indication(s): Chronic Obstructive Pulmonary Disease		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.



**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. (*If not clearly identified by the applicant, this information can usually be derived from annotated labeling.*)

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Proventil aerosol (MDI), Tablet, solution (inhalation)	Toxicology and PK data of albuterol, ipratropium and Combivent. Sections 8 12, and 13 of the PI.
Ventolin aerosol (MDI), tablet, solution (inhalation)	Toxicology and PK data of albuterol, ipratropium and Combivent. Sections 8 12, and Section 13 of the PI.
Combivent CFC	Cross-referenced for non-clinical data

*each source of information should be listed on separate rows

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)
- a. Controlled clinical trial that included PK study comparing Combivent CFC and Combivent Respimat.

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES NO

If “NO,” proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO

If “NO,” proceed to question #5.

If “YES”, list the listed drug(s) identified by name and answer question #4(c).

Ventolin® Inhalation Aerosol

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

Albuterol sulfate

YES

NO

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO

If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Combivent CFC	NDA 20-291	Y
Proventil MDI	NDA 17559	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application: **Combivent CFC**

- b) Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c) Described in a monograph?

YES NO

If "YES", please list which drug(s).

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES NO

If "YES", please list which drug(s) and answer question d) i. below.

If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing: Ventolin and Proventil

i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provides for a change in dosing regimen, from two inhalations four times daily (not to exceed 12 in 24 hours) to one inhalation four times daily (not to exceed 6 in 24 hours) and as a new delivery device.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered YES to question #1, proceed to question #12; if you answered NO to question #1, proceed to question #10 below.

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

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

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

If "**NO**" to (a) proceed to question #11.
If "**YES**" to (a), answer (b) and (c) then proceed to question #12.

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

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?
YES NO

If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

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

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO

If "**NO**", proceed to question #12.

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

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

If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in

the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

- 12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

1. Combivent CFC-MDI/5603918/Expiration date of 06/09/2015

No patents listed *proceed to question #14*

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

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

- No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

21 CFR 314.50(i)(1)(ii): No relevant patents.

21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES NO

If "NO", please contact the applicant and request the signed certification.

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES NO

If "NO", please contact the applicant and request the documentation.

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.

YES NO Patent owner(s) consent(s) to an immediate effective date of approval

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/s/

SADAF NABAVIAN
10/11/2011

**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 and Labeling Review

Date: September 2, 2011

Reviewer: Lissa C. Owens, PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis

Team Leader Carlos Mena-Grillasca, RPh, Team Leader
Division of Medication Error Prevention and Analysis

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

Drug Name(s): Combivent Respimat
(Ipratropium Bromide and Albuterol) Inhalation Spray
20 mcg/100 mcg per actuation

Application Type/Number: NDA 021747

Applicant/sponsor: Boehringer Ingelheim

OSE RCM #: 2011-2325

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

1 INTRODUCTION

This review evaluates the proposed carton labeling and container labels for Combivent Respimat (Ipratropium Bromide and Albuterol) Inhalation Spray 20 mcg/100 mcg, for areas of vulnerability that can lead to medication errors in response to a request from the Division of Pulmonary Allergy and Rheumatology Products (DPARP).

1.1 BACKGROUND OR REGULATORY HISTORY

Combivent Respimat (Ipratropium Bromide and Albuterol) Inhalation Spray is an extension of the Combivent product line. Combivent (NDA 20-291) was approved on October 24, 1996, a chlorofluorocarbon (CFC) metered dose inhaler (MDI). This NDA received a CR letter on August 7, 2009 and is currently on the second review cycle.

DMEPA reviewed and provided recommendations for Combivent Respimat labels and labeling in OSE Review #2008-1954 dated March 24, 2009.

1.2 PRODUCT INFORMATION

The proposed product was developed as a propellant-free replacement in preparation for the eventual removal of the Essential Use Status of Combivent Inhalation Aerosol. Combivent Respimat contains the same combination of an anticholinergic and beta-adrenergic indicated for use in patients with chronic obstructive pulmonary disease (COPD) on a regular aerosol bronchodilator who continue to have evidence of bronchospasm and who require a second bronchodilator. The proposed indication, prescribing population, dosing frequency, and route of administration remain the same as that for Combivent Inhalation Aerosol. However, the dosage is different. The insert labeling indicates that Combivent is to be administered with two inhalations four times daily whereas Combivent Respimat requires *one* inhalation. The recommended dosage is one inhalation four times a day, not to exceed six inhalations in 24 hours. Each dose (1 actuation) delivers 20 mcg ipratropium bromide (monohydrate) and 100 mcg albuterol (equivalent to 120 mcg albuterol sulfate).

The Combivent Respimat cartridge has a net fill weight of 4 grams and when used with the inhaler is designed to deliver at least 120 sprays after preparation for use. When the labeled number of sprays (120) has been dispensed from the inhaler, the Respimat locking mechanism will be engaged and no more sprays can be dispensed.

2 METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis¹ and postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted June 24, 2011
- Carton Labeling submitted June 24, 2011
- Prescribing Information and Instructions for Use submitted June 24, 2011

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

Additionally, since Combivent is currently marketed, DMEPA searched the FDA Adverse Event Reporting System (AERS) database to identify medication errors involving Combivent. The AERS search conducted on August 8, 2011 used the following search terms: trade name “Combiven%”, and the verbatim term “Combiven%.” The reaction terms used were the MedDRA High Level Group Terms (HLGT) “Medication Errors” and “Product Quality Issues”. No time limitations were set.

The reports were manually reviewed to determine if a medication error occurred. Duplicate reports were combined into cases. The cases that described a medication error were categorized by type of error. We reviewed the cases within each category to identify factors that contributed to the medication errors. If a root cause was associated with the label or labeling of the product, the case was considered pertinent to this review. Reports excluded from the case series include those that did not describe a medication error and intentional overdoses.

Following exclusions we had no cases relevant to this review. Additionally, there were no cases involving drug name confusion.

3 RESULTS

The following sections summarize our analysis of the container label, carton and prescribing information labeling.

3.1 GENERAL COMMENTS

On the container labels and carton labeling the manner in which the established name and strength are expressed for the albuterol component appears to be inconsistent. While the strength of the albuterol sulfate component is expressed as the base, the established name is expressed as a salt.

3.2 CARTON LABELING

- The currently marketed Combivent is dosed at 2 inhalations four times daily, whereas Combivent Respimat only requires 1 inhalation four times daily. Since both products will co-exist in the market until Combivent is phased out by December 2013, DMEPA recommends adding a ‘New Dose’ statement to the principal display panel of Combivent Respimat for at least 6 months after the discontinuation of Combivent.
- To further convey the new dosing information and minimize medication errors related to wrong dose, DMEPA recommends revising the Dosage statement from [REDACTED] (b) (4) [REDACTED] to read ‘One inhalation four times a day’.

3.3 PRESCRIBING INFORMATION – INSTRUCTIONS FOR USE

DMEPA’s recommendations on the Instructions for Use section of the PI were discussed with the DRISK/Patient Labeling reviewer and included in their review. We recommended:

- Each step throughout the IFU should be numbered as Step 1, Step 2, etc.
- Each photo should be labeled as Figure A, Figure B, etc.
- In all photos each individual component should be labeled.

4 CONCLUSIONS AND RECOMMENDATIONS

We conclude that the proposed container label and carton labeling introduce vulnerability that could lead to medication errors. We provide recommendations to the Review Division in Section 4.1 and to the Applicant in Section 4.2 to mitigate the risks of such errors. We request these recommendations be communicated to the Applicant prior to approval.

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

4.1 COMMENTS TO THE DIVISION

The manner in which the established name and strength are expressed for the albuterol component is inconsistent. While the strength of the albuterol sulfate component is expressed as the base, the established name is expressed as a salt. DMEPA communicated this observation to the review chemist via email on August 24, 2011, they indicated that “Combivent Respimat (Ipratropium Bromide and Albuterol) Inhalation Spray, 20 mcg/100 mcg would be the better choice” and that they will address this issue in their review. DMEPA defers to Chemistry for final determination with regards to this discrepancy of the established name.

4.2 COMMENTS TO THE APPLICANT

A. All Container labels and Carton labeling

Revise the expression of strength to read “20 mcg/100 mcg” rather than ‘20 and 100 mcg’.

B. Carton labeling

1. On the side panel, relocate the strength statement to appear under the dosage form statement.
2. Add the net quantity statement, “4 grams”, to the principal display panel. Pharmacists typically use the net quantity expressed in grams in computerized systems.
3. Add a ‘New Dose’ statement to the principal display panel to alert patients that this product has a different dosing regimen than the currently marketed Combivent product. We recommend this “New Dose” statement be used for at least 6 months after the discontinuation of Combivent.
4. Revise the Dosage statement to read ‘One inhalation four times a day’ rather than [REDACTED] ^{(b) (4)} The revised statement will reinforce the new dosing regimen for the Combivent Respimat.

5 REFERENCES

OSE Review #2008-1954, Label and Labeling Review for Combivent Respimat (Ipratropium Bromide and Albuterol Sulfate) 20 mcg/100 mcg per actuation, Toyer, Denise. March 24, 2009

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

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/s/

LISSA C OWENS
09/02/2011

CARLOS M MENA-GRILLASCA
09/02/2011

CAROL A HOLQUIST
09/02/2011

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications**

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

Memorandum

Date: August 23, 2011

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

From: Matthew Falter, PharmD, Regulatory Review Officer (DTC)
Roberta Szydlo, R.Ph., Regulatory Review Officer (Professional)
Division of Drug Marketing, Advertising, and Communications
(DDMAC)

CC: Robyn Tyler, DTC Group Leader
Lisa Hubbard, Professional Group Leader
Michael Wade, Regulatory Health Project Manager
Olga Salis, Regulatory Health Project Manager
(DDMAC)

Subject: NDA # 021747
DDMAC labeling comments for Combivent Respimat (ipratropium
bromide and albuterol sulfate) Inhalation Spray

DDMAC has reviewed the proposed Package Insert and proposed Patient's Instructions for Use for Combivent Respimat submitted for consult on June 16, 2011. DDMAC's comments are based on the proposed draft labeling from the sponsor dated August, 5, 2011, which was provided in a link to the EDR sent via email from DPARP to DDMAC on August 11, 2011. This proposed labeling is located at: <\\cdsesub4\NONECTD\NDA021747\4908983>.

DDMAC's comments on the proposed labeling are provided directly in the marked-up document attached (see below).

Please note that DDMAC is not aware of the extent of labeling negotiations which may have occurred with the sponsor during the previous review cycle for this application. Therefore, where appropriate some of our comments in the current review are reiterations of DDMAC's previous recommendations in the review dated May 20, 2009.

Thank you for the opportunity to comment on these proposed materials.

If you have any questions regarding the PI, please contact Roberta Szydlo at (301) 796-5389 or roberta.szydlo@fda.hhs.gov. If you have any questions regarding the Patient's Instructions for Use, please contact Matt Falter at (301) 796-2287 or matthew.falter@fda.hhs.gov.

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/s/

ROBERTA T SZYDLO
08/23/2011

MATTHEW J FALTER
08/23/2011

**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**

Patient Labeling Review

Date: August 11, 2011

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

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Acting Team Leader, Patient Labeling Reviewer
Division of Risk Management (DRISK)

Melissa Hulett, MSBA, BSN, RN
Acting Team Leader, Patient Labeling Reviewer
Division of Risk Management

From: Robin Duer, MBA, BSN, RN
Senior Patient Labeling Reviewer
Division of Risk Management

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

Drug Name: Combivent Respimat (ipratropium bromide and
albuterol sulfate) Inhalation Spray

Application
Type/Number: NDA 21-747

Applicant/sponsor: Boehringer Ingelheim Pharmaceuticals, Inc.

OSE RCM #: 2011-2328

1 INTRODUCTION

On April 7, 2011 Boehringer Ingelheim submitted a Complete Response to FDA's action letter dated August 7, 2009 for a 505(b)(2) new drug application (NDA) for Combivent Respimat (ipratropium bromide and albuterol sulfate) Inhalation Spray. This NDA provided for a new dosage form as a propellant-free replacement for the referenced listed drug and currently marketed Combivent CVC Inhalation Aerosol, NDA 20-291. The new dosage also contains a lower strength dosage.

This review is written in response to a request by the Division of Pulmonary, Allergy and Rheumatology Products (DPARP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Instructions for Use (IFU) for Combivent Respimat (ipratropium bromide and albuterol sulfate) Inhalation Spray.

DRISK conferred with DMEPA on August 8, 2011 and DMEPA deferred to DRISK to provide IFU comments.

2 MATERIALS REVIEWED

- Draft Combivent Respimat (ipratropium bromide and albuterol sulfate) Inhalation Spray Prescribing Information (PI) submitted on April 7, 2011, revised by the Review Division throughout the review cycle and sent to DRISK on August 2, 2011
- Draft Combivent Respimat (ipratropium bromide and albuterol sulfate) Inhalation Spray Instructions for Use (IFU) submitted on April 7, 2011 and sent to DRISK on August 2, 2011

3 REVIEW METHODS

In our review of the IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the IFU is consistent with the PI
- removed unnecessary or redundant information
- ensured that the IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- The enclosed IFU review comments are collaborative DRISK and DMEPA comments.

4 CONCLUSIONS

The proposed IFU is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DRISK on the correspondence.
- Our annotated IFU is appended to this memo. Any additional revisions to the PI should be reflected in the IFU.

Please let us know if you have any questions.

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/s/

ROBIN E DUER
08/11/2011

LASHAWN M GRIFFITHS
08/12/2011

NDA/BLA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

Application Information		
NDA # 21-747 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Combivent Respimat Established/Proper Name: Ipratropium bromide and albuterol sulfate Dosage Form: Inhalation Spray Strengths: 20/100mcg		
Applicant: Boehringer Ingelheim Agent for Applicant (if applicable): Amy Van Ander, DVM, MPH		
Date of Application: 10/07/2008 Date of Receipt: 10/08/2008 Date clock started after UN: N/A		
PDUFA Goal Date: August 08, 2009	Action Goal Date (if different):	
Filing Date: December 19, 2008 Date of Filing Meeting: November 07, 2008		
Chemical Classification: (1,2,3 etc.) (original NDAs only) 3		
Proposed Indication(s): Chronic Obstructive Pulmonary Disease		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>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 defaults to 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 checked="" type="checkbox"/>	<input type="checkbox"/> Drug/Biologic <input checked="" type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device	
<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 (if OTC product):	
List referenced IND Number(s): IND 57,948	
PDUFA and Action Goal dates correct in tracking system? <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established name to the supporting IND(s) if not already entered into tracking system.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are all classification codes/flags (e.g. orphan, OTC drug, pediatric data) entered into tracking system? <i>If not, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Application Integrity Policy	
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ora/compliance_ref/aiplist.html If yes, explain: If yes, has OC/DMPQ been notified of the submission? Comments:	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
User Fees	
Form 3397 (User Fee Cover Sheet) submitted	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
User Fee Status Comments:	<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
<i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. It is expected that all 505(b) applications, whether 505(b)(1) or 505(b)(2), will require user fees unless otherwise waived or exempted (e.g., business waiver, orphan exemption).</i>	
Exclusivity	
Does another product have orphan exclusivity for the same indication? <i>Check the Electronic Orange Book at:</i> http://www.fda.gov/cder/ob/default.htm If yes, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO

<p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i></p> <p>Comments:</p>	
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p> <p>Comments:</p>	<p><input type="checkbox"/> YES # years requested: <input checked="" type="checkbox"/> NO</p>
<p>If the proposed product is a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>):</p> <p>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>	<p><input checked="" type="checkbox"/> Not applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
505(b)(2) (NDAs/NDA Efficacy Supplements only)	
<p>1. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p> <p>2. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).</p> <p>3. 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>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i></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 checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p>

<p>4. Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? <i>Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm</i></p>			<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>If yes, please list below:</p>			
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration
20291	Combivent	5603918	June 09, 2015
<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 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</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> <p>Comments:</p>			<input type="checkbox"/> All paper (except for COL) <input type="checkbox"/> All electronic <input checked="" type="checkbox"/> Mixed (paper/electronic) <input checked="" 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>			<p>Electronic submission: draft carton/container label, draft labeling text, SAS datasets for primary stability data, clinical trial tabulations analysis datasets and case reports.</p>
<p>If electronic submission: <u>paper forms</u> and certifications signed (non-CTD) or <u>electronic forms</u> and certifications signed (scanned or digital signature)(CTD)?</p> <p><i>Forms include: 356h, patent information (3542a), financial disclosure (3454/3455), user fee cover sheet (3542a), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p> <p>Comments:</p>			<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>If electronic submission, does it follow the eCTD guidance? (http://www.fda.gov/cder/guidance/7087rev.pdf)</p> <p>If not, explain (e.g., waiver granted):</p>			<input type="checkbox"/> YES <input type="checkbox"/> NO

<p>Form 356h: Is a signed form 356h included?</p> <p><i>If foreign applicant, both the applicant and the U.S. agent must sign the form.</i></p> <p>Are all establishments and their registration numbers listed on the form?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Index: Does the submission contain an accurate comprehensive index?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:</p> <p><input checked="" type="checkbox"/> legible <input type="checkbox"/> English (or translated into English) <input type="checkbox"/> pagination <input type="checkbox"/> navigable hyperlinks (electronic submissions only)</p> <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Controlled substance/Product with abuse potential:</p> <p>Abuse Liability Assessment, including a proposal for scheduling, submitted?</p> <p>Consult sent to the Controlled Substance Staff?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>BLAs/BLA efficacy supplements only:</p> <p>Companion application received if a shared or divided manufacturing arrangement?</p> <p>If yes, BLA #</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
Patent Information (NDAs/NDA efficacy supplements only)	
<p>Patent information submitted on form FDA 3542a?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Debarment Certification	
<p>Correctly worded Debarment Certification with authorized signature?</p> <p><i>If foreign applicant, both the applicant and the U.S. Agent must</i></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p>sign the certification.</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> <p>Comments:</p>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	
<p>Field Copy Certification: that it is a true copy of the CMC technical section (<i>applies to paper submissions only</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>	<p><input type="checkbox"/> Not Applicable (<i>electronic submission or no CMC technical section</i>)</p> <p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
Financial Disclosure	
<p>Financial Disclosure forms included with authorized signature?</p> <p><i>Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an Agent.</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
Pediatrics	
<p><u>PREA</u></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>Are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES</p> <p><input checked="" type="checkbox"/> NO</p>
<p>If no, is a request for full waiver of pediatric studies OR a request for partial waiver/deferral and a pediatric plan included?</p> <ul style="list-style-type: none"> • <i>If no, request in 74-day letter.</i> • If yes, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) 	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<p>Comments:</p>	

BPCA (NDAs/NDA efficacy supplements only):	
Is this submission a complete response to a pediatric Written Request? <i>If yes, contact PMHS (pediatric exclusivity determination by the Pediatric Exclusivity Board is needed).</i> Comments:	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
Prescription Labeling	
Check all types of labeling submitted. Comments:	<input type="checkbox"/> Not applicable <input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input checked="" type="checkbox"/> Instructions for Use <input type="checkbox"/> MedGuide <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)
Is electronic Content of Labeling submitted in SPL format? <i>If no, request in 74-day letter.</i> Comments:	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Package insert (PI) submitted in PLR format? If no , was a waiver or deferral requested before the application was received or in the submission? If before , what is the status of the request? <i>If no, request in 74-day letter.</i> Comments:	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? Comments:	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
MedGuide or PPI (plus PI) consulted to OSE/DRISK? (<i>send WORD version if available</i>) Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
REMS consulted to OSE/DRISK? Comments:	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
Carton and immediate container labels, PI, PPI, and proprietary name (if any) sent to OSE/DMEDP? Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

OTC Labeling	
<p>Check all types of labeling submitted.</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <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)
<p>Is electronic content of labeling submitted?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Are annotated specifications submitted for all stock keeping units (SKUs)?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>If representative labeling is submitted, are all represented SKUs defined?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Proprietary name, all labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEDP?</p> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
Meeting Minutes/SPA Agreements	
<p>End-of Phase 2 meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES Date(s): 2/6/07 and 4/26/06 <input type="checkbox"/> NO
<p>Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES Date(s): 1/16/08 <input type="checkbox"/> NO
<p>Any Special Protocol Assessment (SPA) agreements?</p> <p><i>If yes, distribute letter and/or relevant minutes before filing meeting.</i></p> <p>Comments: A Response to a Special Protocol Assessment Request was communicated November 08, 2001.</p>	<input type="checkbox"/> YES Date(s): <input checked="" type="checkbox"/> NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: November 07, 2008

NDA/BLA #: 21-747

PROPRIETARY/ESTABLISHED NAMES: Combivent Respimat (Ipratropium bromide/albuterol sulfate)

APPLICANT: BI

BACKGROUND: This NDA provides as a propellant-free replacement for Combivent CFC MDI with the same proposed indication with patients with COPD.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Sadaf Nabavian	Yes
	CPMS/TL:	Sandy Barnes	No
Cross-Discipline Team Leader (CDTL)	Lydia Gilbert-McClain		Yes
Clinical	Reviewer:	Xu Wang	Yes
	TL:	Lydia Gilbert-McClain	Yes
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OSE	Reviewers:	Jinhee Lee Nancy Carothers (OSE/DRISK)	No No
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Partha Roy	Yes
	TL:	Qiu Wei	Yes
Biostatistics	Reviewer:	Ruthi Devi	Yes
	TL:	Qian Li	No
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Luqi Pei	Yes
	TL:	Timothy Robison	Yes
Statistics, carcinogenicity	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Alan Schroeder	No
	TL:	Prasad Peri	Yes
Facility (<i>for BLAs/BLA supplements</i>)	Reviewer:		
	TL:		
Microbiology, sterility (<i>for NDAs/NDA efficacy supplements</i>)	Reviewer:	Brian Riley/Sylvia Gantt RPM @ 6-2123	No
	TL:	Jim Mchey	No
Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Other reviewers	DSI/Susan Thompson/Tejashri Purohit-Sheth		No

OTHER ATTENDEES:

505(b)(2) filing issues? If yes, list issues:	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
Per reviewers, are all parts in English or English translation? If no, explain:	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p>Electronic Submission comments</p> <p>List comments:</p>	<input type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an 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> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<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 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>	<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
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
BIOSTATISTICS Comments:	<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
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments:	<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
PRODUCT QUALITY (CMC) Comments:	<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"> 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:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Establishment(s) ready for inspection? <ul style="list-style-type: none"> Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments: Requested from CMC</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO TBD (By Prasad) <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Sterile product? <p>If yes, was Microbiology Team consulted for</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES

validation of sterilization? (NDAs/NDA supplements only)	<input type="checkbox"/> NO
FACILITY (BLAs only)	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
Comments:	<input type="checkbox"/> Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Division Director	
GRMP Timeline Milestones: PDUFA 08/08/2009	
Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input type="checkbox"/>	Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into tracking system.
<input type="checkbox"/>	If RTF action, notify everybody who already received a consult request, OSE PM., and Product Quality PM. Cancel EER/TBP-EER.
<input type="checkbox"/>	If filed and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	If BLA or priority review NDA, send 60-day letter.
<input type="checkbox"/>	Send review issues/no review issues by day 74
<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.

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

/s/

SADAF NABAVIAN
08/05/2009

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

Division of Pulmonary and Allergy Products

Application Number: NDA 21-747

Name of Drug: Combivent Respimat

Applicant: Boehringer Ingelheim

Material Reviewed:

Submission Date(s): October 07, 2008

Receipt Date(s): October 08, 2008

Submission Date of Structure Product Labeling (SPL): October 07, 2008

Type of Labeling Reviewed: Word/SPL

Background and Summary

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

Review

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

General Comments

1. For specific requirements on the content and format of labeling for human prescription drug and biologic products refer to 21 CFR 201.57. Also see Draft Guidance for Industry: Labeling for human Prescription Drug and Biological Products – Implementing the New Content and Format Requirements (Implementation Guidance).
2. Refer to <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for fictitious examples of labeling format.

Highlights

3. Do not use “TM” or “R” symbols after the drug names in Highlights or the Table of Contents. You can use these symbols once upon first use in the FPI. We recommend this because the symbol will not appear in the SPL version of labeling, and we want the WORD version to match the SPL version as much as possible.

Dosage and Administration

4. The dosage form, “Inhalation spray” should be removed and be included under Dosage Form and Strength. This section should only contain a concise summary of recommended dosage regimen, starting dose, dose range, critical difference among population subsets, monitoring recommendations, other clinically significant clinical pharmacologic information that affects dosing recommendations and if applicable, special storage or handling information.

Dosage Forms and Strengths

5. The subheading “Inhalation spray” should be included in this section.

Use in Specific Populations:

6. This section should be included preceding Drug Interaction section and the following statement should be added: “Pregnancy Category C: based on animal data, may cause fetal harm”. Use only if clearly needed.” If a pregnancy registry exists, state “Pregnancy registry available.” Also this section should be cross-referenced to Pregnancy subsection (8.1)

Full Prescribing Information Contents

7. Dash line located between the Table of Contents and the FPI should be removed and replaced by horizontal line.

Recommendations

Please address the identified deficiencies/issues and re-submit labeling by January 30, 2009. This updated version of labeling will be used for further labeling discussions.

Sadaf Nabavian
Regulatory Health Project Manager

Supervisory Comment/Concurrence:

Sandy Barnes
Chief, Project Management Staff

Drafted: SNabavian/12.11.08

Revised/Initialed: SBarnes/ 12.15.08

Finalized: SNabavian/12.15.08

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

CSO LABELING REVIEW OF PLR FORMAT

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/s/

SADAF NABAVIAN
08/03/2009

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications**

Memorandum

Date: May 20, 2009

To: Carol Hill, Regulatory Health Program Manager

From: Jessica Adams, Regulatory Review Officer, DDMAC
Robyn Tyler, Regulatory Review Officer DDMAC

Subject: NDA 21-747
DDMAC labeling comments for COMBIVENT[®] RESPIMAT[®]
(ipratropium bromide and albuterol sulfate) Inhalation Spray

DDMAC has reviewed the proposed product labeling (PI) and patient product information (PPI) for COMBIVENT[®] RESPIMAT[®] (ipratropium bromide and albuterol sulfate) Inhalation Spray in response to the consult request submitted by the Division of Pulmonary and Allergy Products on October 29, 2008.

The following comments are provided using the version of the proposed PI and PPI in the EDR dated October 07, 2008. We offer the following comments on the PI and PPI.

If you have any questions on the comments for the proposed PI, please contact Jessica Adams at (301) 796-3351 or jessica.adams@fda.hhs.gov.

If you have any questions on the comments for the proposed PPI, please contact Robyn Tyler at (301) 796-4212 or robyn.tyler@fda.hhs.gov

Patient's Instructions for Use:

DDMAC has reviewed the proposed Patient Instructions for Use and notes the following:

The 2nd paragraph, 2nd sentence states. [REDACTED] (b) (4)
[REDACTED] (emphasis added)

- Is it necessary to use the terms [REDACTED] (b) (4) in this context? DDMAC recommends deleting these terms, as they may be used promotionally to imply an advantage over other therapies.
- Is it necessary to include the vague text [REDACTED] (b) (4)? If so, DDMAC suggests providing additional context.

Proposed Product Labeling

DDMAC has reviewed the Proposed Product Labeling and notes our comments on the following pages.

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

1

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

/s/

Jessica Adams
5/20/2009 02:22:41 PM
DDMAC PROFESSIONAL REVIEWER



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

Date: April 21, 2009

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

Through: Jodi Duckhorn, MA, Team Leader
Division of Risk Management

From: Nancy Carothers, RN, BA
Division of Risk Management

Subject: Memo to File Regarding Review of Patient Labeling (Patient Package Insert)

Drug Name(s): COMBIVENT® RESPIMAT® (ipratropium bromide and albuterol sulfate) Inhalation Spray

Application Type/Number: NDA 21-747

Applicant/sponsor: Boehringer Ingelheim Pharmaceuticals, Inc.

OSE RCM #: 2008-1763

Boehringer Ingelheim Pharmaceuticals, Inc. submitted an original New Drug Application, NDA 21-747, for COMBIVENT® RESPIMAT® (ipratropium bromide and albuterol sulfate) Inhalation Spray on October 7, 2008. This submission was for a new dosage form for a propellant-free replacement inhaler for the Combivent CFC Inhalation Aerosol and for a lower strength dosage. COMBIVENT® RESPIMAT® is a combination of an anticholinergic and beta-adrenergic indicated for use in patients with chronic obstructive pulmonary disease (COPD) who are using a regular aerosol bronchodilator but continue to have evidence of bronchospasm and who require a second bronchodilator.

The Division of Pulmonary and Allergy Products (DPAP) requested that the Division of Risk Management review the applicant's proposed COMBIVENT® RESPIMAT® patient package insert, which included Patient Instructions for Use for the COMBIVENT® RESPIMAT® propellant-free inhaler. DPAP will not be addressing labeling at this time. We will not complete our review until such time that DPAP is able to address labeling. If at some point in the future patient directed labeling is resubmitted for COMBIVENT® RESPIMAT®, please send another request for review.

This memo serves to close-out the consult request for COMBIVENT® RESPIMAT® (ipratropium bromide and albuterol sulfate) Inhalation Spray.

Please let us know if you have any questions.

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

/s/

Nancy B Carothers
4/21/2009 10:36:54 AM
DRUG SAFETY OFFICE REVIEWER

Jodi Duckhorn
4/21/2009 10:40:34 AM
DRUG SAFETY OFFICE REVIEWER

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: April 2, 2009

TO: Sabaf Nabavian, Pharm.D., Regulatory Project Manager
Xu Wang, M.D., Medical Officer
Division of Pulmonary and Allergy Products

FROM: Susan D. Thompson, M.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

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

SUBJECT: Evaluation of Clinical Inspections.

NDA: 21-747

APPLICANT: Boehringer Ingelheim Pharmaceutical, Inc.

DRUG: Combivent Respimat Inhalation Spray (ipratropium 20 µg/salbutamol 100 µg)

NME: No

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATIONS: Use in patients with chronic obstructive pulmonary disease (COPD) on a regular aerosol bronchodilator, who continue to have evidence of bronchospasm, and who require a second bronchodilator

CONSULTATION REQUEST DATE: November 13, 2008

DIVISION ACTION GOAL DATE: June 30, 2009

PDUFA DATE: August 8, 2009

I. BACKGROUND:

In response to the U.S. agreement with the global treaty for removal of substances that damage the ozone layer (the Montreal Protocol) calling for CFC phase out of CFC-containing medications, the sponsor has developed the current COMBIVENT[®] formulation. The currently marketed COMBIVENT[®] MDI product on the market is a CFC-containing product and COMBIVENT[®] Respimat[®] was developed to replace it. The proposed rule to ban COMBIVENT[®] CFC (as well as 6 other CFC-containing products) from the market was published in 2007, and the final rule is targeted to be published in June, 2009. The NDA for COMBIVENT[®] Respimat[®] PDUFA date is August 8, 2009, but because of the public health implications, the review team is working to take a regulatory action prior to the PDUFA goal date at mid-cycle (March 8, 2009) given that the proposed rule that will ban the production of COMBIVENT[®] CFC is currently planned to be finalized by June 30, 2009. The proposed indication for COMBIVENT[®] Respimat[®] is the same as COMBIVENT[®] presently holds:

“COMBIVENT[®] Respimat[®] is indicated for use in patients with chronic obstructive pulmonary disease (COPD) on a regular aerosol bronchodilator, who continue to have evidence of bronchospasm, and who require a second bronchodilator.”

A brief synopsis of the protocol which the review division requested to be inspected is given below. This protocol is the sole pivotal study submitted with this NDA.

Protocol 1012.6: A comparison of ipratropium bromide/salbutamol delivered by the Respimat[®] inhaler to COMBIVENT[®] Inhalation Aerosol and ipratropium bromide delivered by the Respimat[®] in a 12-week, double-blind, safety and efficacy study in adults with chronic obstructive pulmonary disease

Protocol 1012.6 was a 12-week, randomized, double-blind, double-dummy, parallel-group, active comparator controlled, multi-center and multi-national trial in patients of either sex, 40 years or older, with a diagnosis of COPD ($FEV_1 \leq 65\%$ predicted normal and $FEV_1/FVC \leq 70\%$). between November, 2006 and May, 2008. Subjects were enrolled at 266 active centers, 179 sites worldwide and 87 study sites inside the United States. The primary objective of the study was to compare the long-term (12 week) bronchodilator efficacy and safety of ipratropium bromide/salbutamol combination administered by the Respimat[®] 20 mcg/100 mcg (one inhalation qid) to ipratropium bromide delivered by the Respimat[®] (20 mcg); one inhalation qid) and COMBIVENT[®] Inhalation Aerosol (two inhalations qid) in patients with COPD.

Inclusion criteria were:

- Diagnosis of COPD meeting the following requirements
 - Have a relatively stable, moderate to severe airway obstruction with pre-bronchodilator $FEV_1 \leq 65\%$ of predicted normal and $FEV_1 \leq 70\%$ of FVC.
- Male or female patients 40 years of age or older
- Smoking history of more than 10 pack-years
- Able to perform pulmonary function tests and maintain records during the study period
- Able to be trained in the proper use of an MDI and Respimat[®] inhaler.

- Sign an informed consent.

Exclusion criteria include:

- Significant diseases other than COPD
- Clinically relevant baseline hematology, blood chemistry, or urinalysis
- All patients with an AST (SGOT) >80 IU/L, ALT (SGPT) >80 IU/L, bilirubin >2.0 mg/dL or creatinine >2.0 mg/dL
- Total eosinophil count $\geq 600/\text{mm}^3$
- History of myocardial infarction within the past year
- Recent history of heart failure or patients with any cardiac arrhythmia requiring drug therapy
- History of cancer, other than treated basal cell carcinoma, within the last five years
- History of life-threatening pulmonary obstruction, cystic fibrosis, or clinically evident bronchiectasis
- History of thoracotomy with pulmonary resection
- History of asthma or allergic rhinitis
- History of and/or active alcohol or drug abuse
- Known active tuberculosis
- Upper or lower respiratory tract infection or COPD exacerbation in the 6 weeks prior to the Screening Visit or during the baseline period
- Known symptomatic prostatic hypertrophy or bladder neck obstruction
- Known narrow-angle glaucoma
- Current significant psychiatric disorders
- Use of daytime oxygen therapy for more than 1 hours per day
- Use of cromolyn sodium or nedocromil sodium less than 30 days prior to the baseline period
- Treatment with antihistamines for any excluded allergic conditions
- Oral corticosteroid medication at unstable doses or at a dose in excess of the equivalent of 10 mg of prednisone per day or 20 mg every other day
- Initiation of inhaled steroid use or new dosage less than 7 weeks prior to the Screening Visit
- Use of beta-blocker medications, MAO inhibitors, or tricyclic antidepressants less than 30 days prior to the baseline period
- Changes in their therapeutic plan within the last 6 weeks prior to the Screening Visit
- Pregnant or nursing women or women of childbearing potential
- Known hypersensitivity to anticholinergic drugs or any other component of the ipratropium bromide/salbutamol Respimat solution
- Previous participation in the study
- Current participation in another study
- Took an investigational drug within 1 month or 6 half lives (whichever is greater)

The initial screening visit was followed by a 2-week baseline run-in period. All patients received ATROVENT[®] MDI (2 puffs, four times a day) and salbutamol MDI (used prn) during

the 2-week baseline period. After the baseline period, patients were randomized into the 12-week double-blind study in which they received one of three treatments:

- Ipratropium bromide/salbutamol inhalation solution (20 mcg/100 mcg) from a Respimat[®] inhaler plus placebo COMBIVENT[®] MDI
- Ipratropium bromide inhalation solution (20 mcg) from a Respimat[®] inhaler plus placebo COMBIVENT[®] MDI
- COMBIVENT[®] Inhalation Aerosol (18 mcg ipratropium bromide monohydrate/103 mcg salbutamol sulfate per inhalation from the mouthpiece) plus placebo inhalation solution from a Respimat[®] inhaler

The duration of treatment was 12 weeks. Subjects were evaluated at Day -30, -14, 1 (\pm 5 days), 29 (\pm 5 days), 57 (\pm 5 days), and 85 (\pm 5 days). On Day -30, informed consent was obtained. On Day -14, a physical examination was performed, and medical history with demographics was recorded. Blood was sampled and screening/qualifying pulmonary function tests (FEV₁ and FVC) were performed. An ECG and MDI training were performed. On Day 1, MDI and Respimat[®] training were completed, pulmonary function testing (PFT) was performed, and study medications were dispensed. On Day 29, PFT was performed, and blood and urine samples for PK testing were collected. On Day 57, PFTs were performed. On Day 85 (the end of study visit), a physical examination and ECG were performed, and PFTs repeated. At all visits, adverse events and concomitant medications were recorded.

The primary criterion for evaluation was measurement of the FEV₁ obtained during PFT; PFTs were obtained at screening, at the end of the 2-week baseline, and every 4 weeks thereafter.

The primary analysis was comparison of FEV₁ AUC across treatment groups using ANCOVA with fixed effects for treatment and investigator site; day -1 baseline was used as a covariate.

The primary comparison was for Day 85. The analysis was repeated for the observation periods zero to 6 hours (FEV₁ AUC_{0-6h}), 0 to 4 hours (FEV₁ AUC_{0-4h}), and 4 to 6 hours (FEV₁ AUC_{4-6h}). The analysis was performed on the set of subjects with baseline data and post-treatment data for the first 3 hours on any test day. An analysis was performed on the Per Protocol population if this population constitutes less than 90% of the full analysis set. The secondary endpoints are the FVC, events from the Patient Daily Record, the daily Peak Expiratory Flow Rate (PEFR), daily rescue medication use, daily symptom assessments, rescue medication on PFT days, COPD exacerbations, and physician global evaluation. Safety analyses included the number of patients with clinically meaningful changes in vital signs from treatment baseline, mean changes in blood pressure and pulse rate from baseline, new ECG or physical examination findings at end of treatment, and trough PEFR morning measurements.

Brief Summary of Results

There were 1480 subjects randomized at 266 centers: 493 in the COMBIVENT[®] Respimat[®] 20/100 mcg group, 498 in the COMBIVENT[®] CFC-MDI 36/206 mcg group, and 489 in the ipratropium Respimat[®] 20 mcg group. Of these, 1460 subjects received study medication. The analysis of the primary endpoints demonstrated that:

- COMBIVENT[®] Respimat[®] 20/100 mcg was non-inferior to COMBIVENT[®] CFC-MDI 36/206 mcg between 0 and 6 hours, on all 7 test days. On Day 85 the mean treatment difference in FEV₁ AUC_{0-6h} was 0.003 L in favor of COMBIVENT[®] CFC-MDI 36/206 mcg (95% confidence interval 0.015 L in favor of COMBIVENT[®] Respimat[®] 20/100 mcg to 0.022 L in favor of COMBIVENT[®] CFC-MDI 36/206 mcg).
- COMBIVENT[®] Respimat[®] 20/100 mcg was superior to ipratropium Respimat[®] 20 mcg between 0 and 4 hours, on all 4 test days (p<0.0001). On Day 85 the mean treatment difference in FEV₁ AUC_{0-4h} in favor of COMBIVENT[®] Respimat[®] 20/100 mcg was 0.047 L (p<0.0001).
- COMBIVENT[®] Respimat[®] 20/100 was non-inferior to ipratropium Respimat[®] 20 mcg between 4 and 6 hours, on all 4 test days. On Day 85 the mean treatment difference in FEV₁ AUC_{4-6h} in favor of ipratropium Respimat[®] 20/100 mcg was 0.017 L (95% confidence interval 0.005 L in favor of COMBIVENT[®] Respimat[®] 20/100 mcg to 0.039 L in favor of ipratropium Respimat[®] 20 mcg).

A total of 164 randomized subjects discontinued treatment prematurely (48 in the COMBIVENT[®] Respimat[®] 20/200 arm, 55 in the COMBIVENT[®] CFC-MDI 36/206 mcg arm, and 61 in the Ipratropium Respimat[®] arm. The most common reason for premature discontinuation was adverse event due to study disease worsening.

Rationale for Site Selection

A single pivotal trial to support the efficacy of this NDA application was submitted. The trial was designed with three co-primary endpoints, two of which are based on demonstration of non-inferiority to active treatment. The quality of trial conduct is critical to the validity of the inferences drawn in non-inferiority trials. In a non-inferiority trial, factors such as poor compliance, missing data, and errors in randomization may make a non-inferiority trial more likely to appear to demonstrate efficacy of an investigational drug even when the investigational drug lacks efficacy. This is due to the fact that the desired outcome in a non-inferiority trial is a lack of difference between study arms. Therefore, the verification of the integrity of the trial is essential to decision-making. The four sites were chosen based on the enrollment of large numbers of study subjects in these sites. Preliminary review of the data has not revealed any irregularities.

II. RESULTS (by Site):

Name of CI, IRB, or Sponsor Location	Protocol #: and # of Subjects:	Inspection Date	Field Classification	Final Classification
Thomas D. Kaelin Lowcountry Lung & Critical Care, PA 9150 B Medcom Street Charleston, SC 29406	Protocol #1012.56 Site # 01037 # of Subjects: 47	1/12- 1/15/09	VAI	Pending
Andras Koser Greenville Pharmaceutical Research 220 Roper Mountain Road Extension, Suite B Greenville, SC 29615	Protocol #1012.56 Site # 01085 # of Subjects: 44	Pending	Pending	Pending
Lon Lynn Clinical Research of West Florida 5115 North Armenia Ave. Tampa, FL 33603	Protocol #1012.56 Site # 01048 # of Subjects: 35	3/3-3/5/09	NAI	Pending
Daniel Lorch PAB Clinical Research 910 Oakton Drive Suite 201 Brandon, FL 33511	Protocol #1012.56 Site # 01058 # of Subjects: 48	2/5-2/13/09	VAI	Pending

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

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

1. Dr. Thomas Kaelin

9150 B Medcom Street

Lowcountry Lung & Critical Care, PA

Charleston, SC 29406

a. What was inspected: The inspection was conducted in accordance with Compliance Program 7348.811. There were 46 subjects screened and 31 subjects were randomized into the study; 30 subjects completed the study. The files of 31 subjects were reviewed during the inspection. The EIR was not available at the time this CIS was written. The observations noted are based on preliminary communications with the FDA field investigator and the Form FDA 483. An inspection summary will be generated if conclusions change upon receipt and review of the final EIR. There were no limitations to the inspection.

b. General observations/commentary: Several deviations from FDA regulations were noted, and a Form FDA 483 was issued for these violations. The

inspection documented that the investigator did not report to the sponsor adverse events in violation of 21 CFR 312.64, did not prepare and maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation in violation of 21 CFR 312.62(b) and did not adhere to the investigational plan in violation of 21 CFR 312.60.

Failure to Report Adverse Events [21 CFR 312.64]

1. According to the Patient Daily Record, Subject #44018 experienced headaches on 8/25/07 and on 9/21-9/22/07. However, the headaches were not reported as adverse events.
2. According to the Patient Daily Record, Subject #47212 experienced headaches on 8/25/07 and 9/3/07 which were not reported as adverse events.

Recordkeeping Violations [21 CFR 312.62(b)]

1. Subject 44110 had Prednisone and Lomotil listed as concomitant medications on the concomitant therapy source document, but not on the corresponding case report form.

Protocol Violations [21 CFR 312.60]

1. The protocol states that administration of oral steroids is permitted for COPD exacerbations for up to 7 days. However, Subject #44091 received a 14 day prescription for Prednisone on 5/22/07.
 2. According to the Patient Daily Record, Subject #44018 experienced headaches on 8/25/07 and on 9/21-9/22/07 and received aspirin. However, the aspirin was not reported as a concomitant medication.
 3. According to the Patient Daily Record, Subject #47212 experienced headaches on 8/25/07 and 9/3/07. Tylenol taken by the subject on 8/25/07 was not reported as a concomitant medication.
- c. **Assessment of data integrity:** Although there were protocol and recordkeeping violations reported from this site, it is unlikely that these errors will impact the final outcome of the study, nor does it appear that the rights, safety, and welfare of any of the randomized subjects was compromised due to these deficiencies. The data from this site appear acceptable for use in support of the NDA.

2. Dr. Andras Koser

**Greenville Pharmaceutical Research
220 Roper Mountain Road Extension, Suite B
Greenville, SC 29615**

- a. **What was inspected:** This inspection has been completed, and no Form FDA 483 was issued. However, no further information is available at this time. **As a Form FDA 483 was not issued at this site, it is unlikely that significant violations affecting data integrity would have been noted.** However, if upon receipt and review of the EIR, this assessment changes, the review division will

be notified expeditiously.

3. Dr. Lon Lynn
5115 North Armenia Ave.
Clinical Research of West Florida
Tampa, FL 33603

a. What was inspected: The inspection was conducted in accordance with Compliance Program 7348.811. There were 35 subjects screened and 22 subjects were enrolled into the study; 19 subjects completed the study. There were no deaths at this site. There was one SAE of metastatic lung cancer which resulted in subject discontinuation; this SAE was considered to be not related to the study drug. Two subjects were discontinued after exclusionary criteria were discovered. The files of 9 subjects were reviewed in-depth during the inspection. Review of these seven records included verification of all Inclusion and Exclusion criteria, screening laboratory tests and ECGs, study tests such as Pulmonary Function Tests (PFTs), adherence to visit protocols, and other procedures outlined in the protocol. The remaining subjects records were reviewed to ensure that the Informed Consent documents contained the required elements. There were no limitations to the inspection. The observations noted are based on the EIR; no Form FDA 483 was issued.

b. General observations/commentary: The field investigator noted that no significant observations were made during this inspection. No informed consent violations were noted during the inspection. COPD diagnosis and compliance with Inclusion Criteria were verified for all subjects. A few discrepancies were noted between the source file PFTs, the CRFs, and the data listing reported by the sponsor to the FDA as described below:

1. PFT results were obtained on a (b) (4) machine. The inspector noted that some FEV₁ results were overridden by an off-site (b) (4) employee. Most (b) (4)-generated changes in FEV₁ were sent by FAX query to the clinical investigator for signature approval.

Medical Officer Comment: The rationale for these practices is given in the Quality Assurance of Spirometry Measurements document included in the Exhibits and appears to be standard for performance of PFTs. The (b) (4) employees were ensuring that the spirometry trials met the ATS specified criteria for reproducibility, among other parameters. This practice is likely to improve the quality of the data submitted to the sponsor. This is not considered a violation.

2. For Subjects # 44415 and #44429, the subject records do not contain the FAX confirmation with the clinical investigator's signature for (b) (4)-amended PFT results.
3. For Subjects #44411 and #44415, the e-diary was not always completed for subject medication compliance. However, the Respimat and MDI compliance contain records of medication compliance.

c. Assessment of data integrity: There do not appear to be significant data integrity or

subject safety issues at this site. The data from this site appear acceptable for use in support of the NDA.

4. **Daniel G. Lorch, Jr., M.D.**
555 Winderley Place, Suite 200
Maitland, FL 32751

- a. What was inspected:** The inspection was conducted in accordance with Compliance Program 7348.811. There were 35 screening failures and 13 subjects were randomized into the study. There were no deaths or SAEs at this site. The files of 7 subjects (three from the beginning of the study, two from the middle of the study, and two from the end of the trial) were reviewed during the inspection. Review of these seven records included verification of all inclusion and exclusion criteria, a review of each scheduled visit with comparison of the data from each of those visits to the source records, to the CRFs, and to the reports provided from the sponsor to the center. The remaining six subject records were reviewed to ensure that each subject completed the study, was appropriately issued an informed consent document, and met the Inclusion/Exclusion criteria established in the protocol. There were no limitations to the inspection. The observations noted are based on the Form FDA 483 and the EIR.
- b. General observations/commentary:** Several deviations from FDA regulations were noted, and a Form FDA 483 was issued for these violations. The inspection documented that the investigator did not adhere to the investigational plan, in violation of 21 CFR 312.60, did not prepare and maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation in violation of 21 CFR 312.62(b), and did not maintain adequate records of the disposition of the drug in violation of 21 CFR 312.62(a). The following violations were noted:

Protocol Violations [21 CFR 312.60]

Subjects were allowed to enter and complete the study despite the presence of potential exclusionary criteria which were either not confirmed or excluded.

1. Subject #44715 (b) (6) had the Inclusion/Exclusion criterion page of the CRF missing.
2. Subject #47254 (b) (6) was included in the study with hematuria and the site failed to verify that the subject did not have cancer after the site requested this evaluation.
3. Subject #44725 (b) (6) used Advair 250/50, an inhaled steroid.
4. Subject #47252 (b) (6) started Nasacort AQ for a deviated septum and omeprazole for GERD in 2007, with no indication that they were on these medications for at least six weeks prior to entering the study as required by the protocol.
5. The protocol states that patients must be able to maintain records during the study as an inclusion criterion. An e-diary entry dated 7/26/07 for

Subject #44725 (b) (6) documented diary compliance to be 89% at visit 2. A note stated that the subject was retrained on the device. At visit 3, the e-diary data report documented that the patient did not report any medication dosages in the diary, with no documentation of correspondence with the sponsor for approval of the subject's continued participation in the study.

Recordkeeping Violations [21 CFR 312.62(b)]

The following subjects had missing records and/or documentation:

1. Subject #44715 (b) (6) was missing the page for Inclusion/Exclusion criteria in the CRF.
2. Subject # 47252 (b) (6), #44722 (b) (6), and #44725 (b) (6) were missing CRF washout verification documentation forms for visit 4.
3. Subject #47256 (b) (6) was missing the washout verification documentation for visits 4 and 5.

Inadequate Drug Disposition Records [21 CFR 312.62(a)]

The drug accountability records for albuterol and an albuterol HFA Master Log for this site documented that 46 inhalers were received by the site from the sponsor. The sponsor drug accountability records listed above also documented that 7 inhalers were returned full, 5 were missing, and 34 were returned partially full (for a total of 46).

Review of the site's individual subject dispensing logs revealed that 28 inhalers were dispensed to the 13 randomized subjects, 5 were dispensed to screen failure subjects, and 5 were dispensed to screen failure subjects during the two-week baseline run-in period (for a total of 33 partially full inhalers). Accountability records did not document the disposition of the additional inhaler returned partially full or the 5 missing inhalers as documented by the sponsor.

There were several items discussed with Dr. Lorch at the conclusion of the inspection which were not cited in the Form FDA 483, as listed below:

1. The storage room was monitored for temperature. However, there were six days during the study where no monitoring was recorded, and there was no documentation that the thermometer was calibrated during the study period.
2. (b) (4) was the company used to calibrate study equipment, including sphygmomanometers. However, (b) (4) was not certified for this calibration function. In addition the calibration of the sphygmomanometers did not include documentation of pre- and post-calibration results.
3. The concomitant therapy sheets were to be updated at each study visit. However, the concomitant therapy records do not reflect when they were annotated or who annotated them.
4. For Subjects #44715, 44716, 47252, and 47256 there was inadequate history recorded regarding alcohol intake.

5. For Subjects #47252 and #47256, the Inclusion/Exclusion criteria worksheets were signed off as accepted prior to the results of the confirmatory tests being received.
6. PFT results were obtained on a (b) (4) machine. The inspector noted that some FEV₁ results were overridden by an off-site (b) (4) employee. Most Viasys-generated changes in FEV₁ were sent by FAX query to the clinical investigator for signature approval.

Medical Officer Comment: The rationale for these practices is given in the Quality Assurance of Spirometry Measurements document included in the Exhibits and appears to be standard for performance of PFTs. The (b) (4) employees were ensuring that the spirometry trials met the ATS specified criteria for reproducibility, among other parameters. This practice is likely to improve the quality of the data submitted to the sponsor. This is not considered a violation.

- c. **Assessment of data integrity:** Although there were protocol, recordkeeping, and drug disposition record violations reported from this site, it is unlikely that these errors will impact the final outcome of the study. The data from this site appear acceptable for use in support of the NDA.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

In general, inspection of the sites of Drs. Kaelin, Koser, Lynn, and Lorch revealed that they adhered to the applicable regulations and good clinical practices governing the conduct of clinical investigations. The inspections of documents at the sites of Drs. Kailin, Lynn, and Lorch supports that audited subjects exist, met eligibility criteria, received assigned study medication, adhered to the protocol, and signed informed consent documents; detailed results of the inspection of Dr. Koser's site are pending. The inspections documented minor regulatory violations at the sites of Drs. Kailin and Lorch. In general, the studies at these sites appear to have been conducted adequately, and the data generated by all four sites may be used in support of the indication.

Follow-Up Actions: All observations at Dr. Kaelin's site are based on preliminary communications with the FDA filed investigators and the Form FDA 483. In addition, no information is available regarding the inspection of Dr. Koser other than a Form FDA 483 was not issued. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

{See appended electronic signature page}

Susan D. Thompson, M.D.
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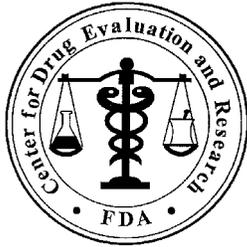
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date: March 24, 2009

To: Badrul Chowdhury, MD, Director
Division of Pulmonary and Allergy Products

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

From: Denise Toyer, PharmD, Deputy Director
Division of Medication Error Prevention and Analysis

Subject: DMEPA Label and Labeling Review

Drug Name: Combivent Respimat
(Ipratropium Bromide and Albuterol Sulfate) Inhalation Spray
20 mcg/100 mcg per actuation

Application Type/Number: NDA # 21-747

Applicant/Applicant: Boehringer Ingelheim Pharmaceuticals, Inc.

OSE RCM #: 2008-1954

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EXECUTIVE SUMMARY

The Division of Medication Error Prevention and Analysis (DMEPA) noted areas of vulnerability that could lead to medication errors with the proposed container labels, carton and insert labeling of Combivent Respimat. Improvements that could be made involve the prominence, presentation, and consistency of information that is vital to the safe use of the product. DMEPA believes the risks we have identified can be addressed and mitigated prior to drug approval, and provides recommendations in Section 5 that aim at reducing the risk of medication errors.

1 BACKGROUND

1.1 INTRODUCTION

This review was written in response to a request from the Division of Pulmonary and Allergy Products to review the Applicant's container labels, carton and insert labeling.

1.2 REGULATORY HISTORY

Combivent Respimat (Ipratropium Bromide and Albuterol Sulfate) is an extension of the Combivent product line. Combivent (NDA 20-291) was approved on October 24, 1996, a chlorofluorocarbon (CFC) metered dose inhaler (MDI). The proposed product was developed as a propellant-free replacement in preparation for the eventual removal of the Essential Use Status of Combivent Inhalation Aerosol. The proposed indication, prescribing population, dosing frequency and route of administration remain the same as that for Combivent Inhalation Aerosol. However, the dosage is different. The insert labeling indicates that Combivent is to be administered with two inhalations four times daily whereas Combivent Respimat requires one inhalation.

The proposed proprietary name was evaluated under a separate cover in a DMEPA proprietary name review managed under the same review number (OSE 2008-1954) dated February 5, 2009.

1.3 PRODUCT INFORMATION

Combivent Respimat is the proposed name for Ipratropium Bromide and Albuterol Sulfate. Combivent Respimat is a combination of an anticholinergic and beta-adrenergic indicated for use in patients with chronic obstructive pulmonary disease (COPD) on a regular aerosol bronchodilator who continue to have evidence of bronchospasm and who require a second bronchodilator.

The Combivent Respimat cartridge has a net fill weight of 4 grams and when used with the inhaler, is designed to deliver at least 120 sprays after preparation for use. When the labeled number of sprays (120) has been dispensed from the inhaler, the Respimat locking mechanism will be engaged and no more sprays can be dispensed.

The recommended dosage is one inhalation four times a day, not to exceed six inhalations in 24 hours. Each dose (1 actuation) delivers 20 mcg ipratropium bromide (monohydrate) and 100 mcg albuterol (equivalent to 120 mcg albuterol sulfate).

2 METHODS AND MATERIALS

This section describes the methods and materials used by DMEPA conducting a label, labeling, and/or packaging risk assessment. The primary focus of the assessment is to identify and remedy potential sources of medication error prior to drug approval. DMEPA defines a medication error as any

preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.¹

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The container label and carton labeling communicate critical information including proprietary and established name, strength, dosage form, container quantity, expiration, and so on. The insert labeling is intended to communicate to practitioners all information relevant to the approved uses of the drug, including the correct dosing and administration.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the Institute for Safe Medication Practices Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.²

Because the DMEPA staff analyzes reported misuse of drugs, the DMEPA staff is able to use this experience to identify potential errors with all medications similarly packaged, labeled or prescribed. DMEPA uses Failure Mode and Effects Analysis (FMEA) and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provide recommendations that aim at reducing the risk of medication errors.

DMEPA reviewed the following labels and labeling submitted by the Applicant on October 7, 2008. We also reviewed the labels and labeling for the currently marketed product, Combivent, submitted in their annual report dated November 25, 2008. See Appendices A through D for pictures of the labels and labeling.

- Combivent Respimat Container Labels (Inhaler and Cartridge)
- Combivent Respimat Carton Labeling
- Package Insert Labeling (no image)
- Patient Instructions for Use (no image)

3 RESULTS

3.1 GENERAL COMMENTS

The established name does not have prominence commensurate with the prominence of the proprietary name.

The proposed labels and labeling resemble the existing labels and labeling for the Applicant's currently marketed product, Combivent. Both labels and labeling utilize identical layouts, fonts, and color schemes (orange and green).

On the container labels and carton labeling, the manner in which the established name and strength are expressed appears to be inconsistent. While the strength of the albuterol sulfate component is expressed as the base, the established name is expressed as a salt. We further note that in the Applicant's already existing product, Combivent, the albuterol component is expressed as the salt only.

The strength does not appear prominent on the labels and labeling.

¹ National Coordinating Council for Medication Error Reporting and Prevention. <http://www.nccmerp.org/aboutMedErrors.html>. Last accessed 10/11/2007.

² Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

3.2 CONTAINER LABELS

See General Comments.

The direction, “turn”, located on the bottom of the inhaler container label does not appear very prominent.

3.3 CARTON LABELING

See General Comments.

3.4 PACKAGE INSERT LABELING

DMEPA has no comments.

3.5 PATIENT INSTRUCTIONS FOR USE

DMEPA defers comments to the Division of Risk Management.

4 DISCUSSION

4.1 LACK OF PROMINENCE AND LOCATION OF STRENGTH STATEMENT

The strength statement (i.e. XX mcg per actuation) is not prominent as it appears embedded in the text of the labels and labeling. Healthcare practitioners need to be able to identify the amount of drug per actuation. This strength statement should appear immediately following or below the established name.

4.2 PROMINENCE OF ESTABLISHED NAME

Although the font size of the established name appears ½ the size of the proprietary name, it does not have a prominence commensurate with the prominence of the proprietary name. It does not take into account all pertinent factors, including typography, layout, contrast, and other printing features. The disparity in size may be attributed to the outlining of the proprietary name which increases the prominence of the name. Thus, this presentation is not in accordance with 21 CFR 201.10(g)(2).

4.3 LAYOUT AND COLOR SCHEMES OF LABELS AND LABELING

The proposed labels and labeling resemble the existing labels and labeling for the Applicant’s currently marketed product, Combivent. Both products utilize identical layouts and color schemes (see picture). Although the two products have overlapping active ingredients, indication, route of administration, frequency of administration, and dosage form, they differ with respect to dosage. The proposed product requires half the number of inhalations of the already existing Combivent product. The recommended dosage for Combivent Respimat is one inhalation four times daily whereas Combivent is two inhalations four times daily.



Given the visual similarities of these cartons, it is easy to see how these two products would be confused for one another. Moreover, since both products will be marketed together for a period of time, these two Combivent products are likely to be stored next to each other on the pharmacy shelf. In order to decrease the potential for selection error, we suggest utilizing a different background color scheme for the proposed product, Combivent Respimat, ensuring that the colors of the two products are distinct.

4.4 EXPRESSION OF ESTABLISHED NAME AND DOSAGE FORM ON CONTAINER/BLISTER LABELS AND BLISTER CARTON LABELING

The strength of this product is expressed based on the active moiety Albuterol and not the salt Albuterol Sulfate. Thus, the established name should be expressed as ‘Albuterol’ or the strength should be expressed as the salt to match the dosage form strength. These comments are consistent with recommendations provided per our e-mail communication with the assigned Chemist from the Office of New Drug Quality Assessment (ONDQA) on January 7, 2009.

Thus, the established name and strength should match and appear as follows:

Combivent Respimat (Ipratropium Bromide and Albuterol Sulfate) Inhalation Spray, 20 mcg/120 mcg

Moreover, the Applicant may indicate what 120 mcg of Albuterol Sulfate is equivalent to in terms of free albuterol base (100 mcg).

4.5 INSTRUCTIONS PRESENT ON INHALER CONTAINER LABEL

The direction to “turn” appears at the bottom of the container label and is not very prominent (see picture). We are concerned that this direction may not be visible enough for the user to see. In addition to its current location, the Applicant may want to consider placing the direction “turn” and the arrows on the principal display panel.



5 CONCLUSIONS AND RECOMMENDATIONS

The Label and Labeling Risk Assessment findings indicate that the presentation of information on the proposed container labels, carton and insert labeling introduces vulnerability to confusion that could lead to medication errors. Specifically, DMEPA notes problems with the prominence, presentation, and consistency of information that is vital to the safe use of the product. DMEPA believes the risks we have identified can be addressed and mitigated prior to drug approval, and provides recommendations in Section 5.2 that aim at reducing the risk of medication errors.

5.1 COMMENTS TO THE DIVISION

DMEPA concurs with ONDQA chemist on the presentation of the established name: Combivent Respimat (Ipratropium bromide and Albuterol sulfate) Inhalation Spray, 20 mcg/120 mcg. For further guidance, DMEPA recommends that the Division consult Richard Lostritto, Chair of the CDER Labeling and Nomenclature Committee (LNC), Deborah Desmer (the Project Manager assigned to the LNC) and the assigned ONDQA Chemist regarding the expression of the established name and strength.

We defer comments regarding the Patient Package Insert/Medication Guide to the Division of Risk Management. Please refer to their forthcoming review (OSE Review #2008-1763).

We would appreciate feedback of the final outcome of this review. We would be willing to meet with the Division for further discussion, if needed. Please copy DMEPA on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Sean Bradley, OSE project manager, at 301-796-1332.

5.2 COMMENTS TO THE APPLICANT

Based upon our assessment of the labels and labeling, DMEPA identified the following areas of needed improvement.

A. All Labels and Labeling

1. Although the font size of the established name appears ½ the size of the proprietary name, it does not have a prominence commensurate with the prominence of the proprietary name. It does not take into account all pertinent factors, including typography, layout, contrast, and other printing features. Revise the labels and labeling to increase the prominence of the established name in accordance with 21 CFR 201.10(g)(2).
2. Revise the color scheme for the proposed product, Combivent Respimat, ensuring that the colors for this product are distinct from the currently marketed Combivent product in order to decrease the potential for selection error.
3. Increase the prominence of the product strength (i.e. XX mcg per actuation), ensuring that it appears immediately following or below the established name.

B. Container Labels and Carton Labeling

Consider adding the direction to “turn” and the arrows already present on the back panel of the inhaler container label to the principal display panel. Inserting these items onto the front panel may help to increase the visibility of this instruction. Additionally, space permitting, consider designing labels that would include the instructions on the inhaler device, to reinforce the instructions on the carton labeling.

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/s/

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