

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
021747Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 21747

SUPPL #

HFD #

Trade Name Combivent Respimat

Generic Name Ipratropium bromide/albuterol Inhalation Spray

Applicant Name Boehringer Ingelheim Pharmaceuticals, Inc.

Approval Date, If Known October 07, 2011

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES NO

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

505(b)(2)

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

YES NO

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

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

d) Did the applicant request exclusivity?

YES NO

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

3 years

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

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

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

NDA#

NDA#

NDA#

2. Combination product.

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

YES NO

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

NDA# 20291	Combivent CFC
NDA# NDA 17559	Proventil Inhalation
NDA 17853	Proventil Tablets
NDA 19243	Proventil Inhalation Solution
NDA# NDA 18473	Ventolin Inhalation
NDA 19112	Ventolin tablets
NDA 19269	Ventolin inhalation solution

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a)

is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

IND 57948 (trial no. 1012.56 (efficacy), trial no. 1012.46 and 1012.62 (safety))

(b) (4) (trial no. 243.7 (dose selection))

(b) (4) (trial no. 244.2447 (dose selection))

Trial no. 244.2484 (non-IND study for Patient Use Information)

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

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

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

Investigation #1 YES NO

Investigation #2 YES NO

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

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

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

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

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

Investigation #1 !
!
IND # 57948 YES ! NO
! Explain:

Investigation #2 !
!
 (b) (4)
YES ! NO
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !
!
YES ! NO
Explain: ! Explain:
Trial 244.2484 (non-IND study)

Investigation #2 !
!
YES ! NO
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

=====

Name of person completing form: Sadaf Nabavian
Title: Regulatory Project Manager
Date: September 26, 2011; October 06, 2011

Name of Office/Division Director signing form: Badrul A. Chowdhury
Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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
10/11/2011

BADRUL A CHOWDHURY
10/11/2011

NDA 21-747

Combivent® Respimat® (ipratropium bromide and albuterol sulfate) Inhalation Spray

DEPARTMENT CERTIFICATION

Certification Requirement Section 306(k)(1) of the Act 21 U.S.C. 355a(k)

Boehringer Ingelheim Pharmaceuticals, Inc. 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.

Signature:

Joanne Palmisano

Name of Applicant:

Joanne Palmisano, M.D.
Vice President, Drug Regulatory Affairs
Boehringer Ingelheim Pharmaceuticals, Inc.

Date:

8 March 2011

Mailing Address:

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

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DEPARTMENT CERTIFICATION

Certification Requirement Section 306(k)(1) of the Act 21 U.S.C. 355a(k)

Boehringer Ingelheim Pharmaceuticals, Inc. 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.

Signature:

Christopher Corsico

Name of Applicant:

Christopher Corsico, M.D.
Vice President, Drug Regulatory Affairs
Boehringer Ingelheim Pharmaceuticals, Inc.

Date:

19 September 2008

Mailing Address:

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

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PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

DA/BLA#: 21-747 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____
Division Name: Pulmonary and Allergy Products PDUFA Goal Date: August 08, 2009 Stamp Date: 10/7/2008
Proprietary Name: Combivent Respimat
Established/Generic Name: Ipratropium bromide/albuterol sulfate
Dosage Form: Inhalation Spray
Applicant/Sponsor: Boehringer Ingelheim

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) _____
(2) _____
(3) _____
(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: COPD

Q1: Is this application in response to a PREA PMR? Yes Continue
No Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMR #: _____

Does the division agree that this is a complete response to the PMR?

- Yes. Please proceed to Section D.
 No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW active ingredient(s) (includes new combination); indication(s); dosage form; dosing regimen; or route of administration?*

(b) No. PREA does not apply. **Skip to signature block.**

* **Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

Q3: Does this indication have orphan designation?

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

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
 No: Please check all that apply:
 Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 Deferred for some or all pediatric subpopulations (Complete Sections C)
 Completed for some or all pediatric subpopulations (Complete Sections D)
 Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (check, and attach a brief justification for the reason(s) selected)

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

			Reason (see below for further detail):				
	minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (check reason corresponding to the category checked above, and attach a brief justification):

Not feasible:

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):			Reason for Deferral			Applicant Certification †
Population	minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

Attachment A

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

.dication #2: _____

Q1: Does this indication have orphan designation?

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

Q2: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
- Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 - Deferred for some or all pediatric subpopulations (Complete Sections C)
 - Completed for some or all pediatric subpopulations (Complete Sections D)
 - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 - Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- Necessary studies would be impossible or highly impracticable because:
- Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

 Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):
ote: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):					
		minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

Necessary studies would be impossible or highly impracticable because:

- Disease/condition does not exist in children
- Too few children with disease/condition to study
- Other (e.g., patients geographically dispersed): _____

*** Not meaningful therapeutic benefit:**

Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so,

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

ection C: Deferred Studies (for some or all pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
				Population	minimum	maximum	Ready for Approval in Adults
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

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

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

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

(Revised: 6/2008)

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 21747 (resubmission) BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Combivent Respimat Established/Proper Name: Ipratropium bromide and albuterol sulfate Dosage Form: Inhalation Spray		Applicant: Boehringer Ingelheim Agent for Applicant (if applicable): Amy Van-
RPM: Sadaf Nabavian		Division: Pulmonary, Allergy, and Allergy Products
<p><u>NDA's:</u> NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p>		<p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u> Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)):</p> <p>NDA 20-983 Albuterol Sulfate HFA NDA 20-291 Combivent CFC-MDI NDA 17559, Proventil MDI NDA 17853 Proventil tablet NDA 19243 Proventil inhalation solution NDA 18473, Ventolin MDI NDA 19112, Ventolin tablet NDA 19269, Ventolin inhalation solution</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>The proposed product is developed as a different device as a propellant-free replacement of the Combivent CFC-MDI.</p> <p><input type="checkbox"/> If no listed drug, check here and explain:</p> <p>Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.</p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p> <p>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</p>
❖ User Fee Goal Date: October 07, 2011 Action Goal Date (if different)		October 07, 2011
❖ Actions		Approval

¹ The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

<ul style="list-style-type: none">Proposed action	<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
<ul style="list-style-type: none">Previous actions (<i>specify type and date for each action taken</i>)	<input type="checkbox"/> None CR: 08/07/2009
❖ Promotional Materials (<i>accelerated approvals only</i>) Note: If accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see guidance www.fda.gov/cder/guidance/2197dft.pdf). If not submitted, explain _____	<input type="checkbox"/> Received N/A

❖ Application ² Characteristics	
Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC Comments: _____	
❖ Date reviewed by PeRC (<i>required for approvals only</i>) If PeRC review not necessary, explain:	July 08, 2009 (Pediatric Waiver Granted due to indication of COPD)
❖ BLAs only: <i>RMS-BLA Product Information Sheet for TBP</i> has been completed and forwarded to OBPS/DRM (<i>approvals only</i>)	<input type="checkbox"/> Yes, date
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)	N/A
• Office of Executive Programs (OEP) liaison has been notified of action	<input type="checkbox"/> Yes <input type="checkbox"/> No
• Press Office notified of action (by OEP)	<input type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information dissemination are anticipated	<input type="checkbox"/> None <input checked="" type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

² All questions in all sections pertain to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes (Double check w/Sandy) If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input checked="" type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input checked="" type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> 	<input checked="" type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified (Double check w/Sandy)

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

N/A

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "**No**," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "**No**," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
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CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ³	September 26, 2011
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Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input type="checkbox"/> Included N/A

Action Letters

❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) CR: 08/07/2009 AP: 10/07/2011
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Labeling

❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	09.27.2011
<ul style="list-style-type: none"> • Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version) 	10.06.2011
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	04.07.2011
<ul style="list-style-type: none"> • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	
❖ Medication Guide/Patient Package Insert/Instructions for Use (<i>write submission/communication date at upper right of first page of each piece</i>)	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input checked="" type="checkbox"/> Instructions for Use <input type="checkbox"/> None

³ Fill in blanks with dates of reviews, letters, etc.
Version: 9/5/08

<ul style="list-style-type: none"> • Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	
<ul style="list-style-type: none"> • Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version) 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	
<ul style="list-style-type: none"> • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	
<ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date at upper right of first page of each submission</i>) 	
<ul style="list-style-type: none"> • Most-recent division proposal for (only if generated after latest applicant submission) 	
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling 	10.07.2001
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input checked="" type="checkbox"/> RPM 08/03/2009 <input checked="" type="checkbox"/> DMEPA02/06/2009, 09/02/2011 <input checked="" type="checkbox"/> DRISK 08/12/2011 <input checked="" type="checkbox"/> DDMAC 05/20/2009, 08/23/2011 <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Review(s) (<i>indicate date(s)</i>) • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) 	02/06/2009, 06/24/2009 09/22/2011 09/22/2011
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) 	505(b)(2) Assessment; 08/05/2009
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	<input checked="" type="checkbox"/> Included N/A
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents www.fda.gov/ora/compliance_ref/aip_page.html 	N/A
<ul style="list-style-type: none"> • Applicant in on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatric Page (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" type="checkbox"/> Included N/A Full Waiver
<ul style="list-style-type: none"> ❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>) 	<input checked="" type="checkbox"/> Verified, statement is acceptable
<ul style="list-style-type: none"> ❖ Postmarketing Requirement (PMR) Studies 	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> • Outgoing communications (<i>if located elsewhere in package, state where located</i>) 	
<ul style="list-style-type: none"> • Incoming submissions/communications 	
<ul style="list-style-type: none"> ❖ Postmarketing Commitment (PMC) Studies 	<input checked="" type="checkbox"/> None

⁴ Filing reviews for other disciplines should be filed behind the discipline tab.
Version: 9/5/08

<ul style="list-style-type: none"> Outgoing Agency request for postmarketing commitments (<i>if located elsewhere in package, state where located</i>) 	
<ul style="list-style-type: none"> Incoming submission documenting commitment 	
❖ Outgoing communications (<i>letters (except previous action letters), emails, faxes, telecons</i>)	Ackn letter: 04/22/2011 IR:09/02/2011
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
<ul style="list-style-type: none"> PeRC (<i>indicate date; approvals only</i>) 	<input type="checkbox"/> Not applicable
<ul style="list-style-type: none"> Pre-Approval Safety Conference (<i>indicate date; approvals only</i>) 	<input checked="" type="checkbox"/> Not applicable
<ul style="list-style-type: none"> Regulatory Briefing (<i>indicate date</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> Pre-NDA/BLA meeting (<i>indicate date</i>) 	<input type="checkbox"/> No mtg January 16, 2008
<ul style="list-style-type: none"> EOP2 meeting (<i>indicate date</i>) 	<input type="checkbox"/> No mtg February 06, 2007
<ul style="list-style-type: none"> Other (e.g., EOP2a, CMC pilot programs) 	11/08/2001 , 05/28/09, 02/22/2010
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> Date(s) of Meeting(s) 	
<ul style="list-style-type: none"> 48-hour alert or minutes, if available 	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 08/07/2009; 09/26/2011 (Draft)
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 08/04/2009; 09/19/2011
Clinical Information⁵	
❖ Clinical Reviews	
<ul style="list-style-type: none"> Clinical Team Leader Review(s) (<i>indicate date for each review</i>) 	Concurred on MO's review
<ul style="list-style-type: none"> Clinical review(s) (<i>indicate date for each review</i>) 	11/18/2008; 07/06/2009; 05/11/2011; 08/20/2011
<ul style="list-style-type: none"> Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> None
❖ Safety update review(s) (<i>indicate location/date if incorporated into another review</i>)	No safety update is required. See MO Rev 7.6.9, page 55 (07/6/2009); Long term safety study required. See MO Rev 1.1, pg 6.
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	MO's Rv 4.6, page 19 MO's Rv 3.3, page 13: 8/20/2011
❖ Clinical reviews from other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not needed
❖ Risk Management <ul style="list-style-type: none"> Review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) REMS Memo (<i>indicate date</i>) 	<input checked="" type="checkbox"/> None

⁵ Filing reviews should be filed with the discipline reviews.
Version: 9/5/08

<ul style="list-style-type: none"> REMS Document and Supporting Statement (<i>indicate date(s) of submission(s)</i>) 	
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input type="checkbox"/> None requested 04/03/09, 06/04/09
Clinical Microbiology <input type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None See concurrence of review
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 07/14/2009
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None Concurrence provided to CP's Review: 08/24/2011
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 12/08/08, 06/02/2009, 08/24/2011
❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of DSI letters</i>)	<input type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
<ul style="list-style-type: none"> ADP/T Review(s) (<i>indicate date for each review</i>) 	<input type="checkbox"/> None
<ul style="list-style-type: none"> Supervisory Review(s) (<i>indicate date for each review</i>) 	<input type="checkbox"/> None 06/08/2009. Also see concurrence of reviews: 06/14/2011; 05/04/2011, 09/06/2009
<ul style="list-style-type: none"> Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>) 	<input type="checkbox"/> None 12/09/08; 03/31/2009; 04/14/09; 05/28/09; 05/04/2011; 06/14/2011
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (<i>include copies of DSI letters</i>)	<input checked="" type="checkbox"/> None requested
CMC/Quality <input type="checkbox"/> None	
❖ CMC/Quality Discipline Reviews	
<ul style="list-style-type: none"> ONDQA/OBP Division Director Review(s) (<i>indicate date for each review</i>) 	<input type="checkbox"/> None
<ul style="list-style-type: none"> Branch Chief/Team Leader Review(s) (<i>indicate date for each review</i>) 	<input type="checkbox"/> None Concurrence on CMC's Review 08/05/2009
<ul style="list-style-type: none"> CMC/product quality review(s) (<i>indicate date for each review</i>) 	<input type="checkbox"/> None 11/12/08, 6/10/09, 08/26/2011, 09/26/2011
<ul style="list-style-type: none"> BLAs only: Facility information review(s) (<i>indicate dates</i>) 	<input type="checkbox"/> None

<ul style="list-style-type: none"> ❖ Microbiology Reviews <ul style="list-style-type: none"> • NDAs: Microbiology reviews (sterility & pyrogenicity) <i>(indicate date of each review)</i> • BLAs: Sterility assurance, product quality microbiology <i>(indicate date of each review)</i> 	06/24/2009 <input type="checkbox"/> Not needed
<ul style="list-style-type: none"> ❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i> 	<input type="checkbox"/> None 3/31/09
<ul style="list-style-type: none"> ❖ Environmental Assessment (check one) (original and supplemental applications) 	Claimed exclusion
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	6/10/09
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	N/A
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	N/A
<ul style="list-style-type: none"> ❖ NDAs: Methods Validation 	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed
<ul style="list-style-type: none"> ❖ Facilities Review/Inspection 	
<ul style="list-style-type: none"> • NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date)</i> 	Date completed: 09/09/2011 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
<ul style="list-style-type: none"> • BLAs: <ul style="list-style-type: none"> ○ TBP-EER ○ Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) <i>(date completed must be within 60 days prior to AP)</i> 	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation Date completed: <input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold

Appendix A to Action Package Checklist

An NDA or NDA supplemental 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) **Or** 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.
- (3) **Or** 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) **And** 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.
- (3) **And** 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) **Or** 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.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

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

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/s/

SADAF NABAVIAN
10/11/2011



Food and Drug Administration
Center for Drug Evaluation and Research

1. Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: September 27, 2011

To: Amy Van Andel	From: Sadaf Nabavian
Company: BI	Division of Pulmonary, Allergy and Rheumatology Products
FAX number: 203-791-6262	Fax number: 301-796-9728
Phone number: 203-798-5452	Phone number: 301-796-2777

Subject: Combivent Respimat

Total Number of Pages Including Cover: 5

Comments: Labeling comments

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.

NDA 21747
Combivent Respimat
BI

Dear Dr. Van Andel:

We are reviewing your resubmission dated April 7, 2011, for Combivent Respimat (ipratropium bromide/albuterol sulfate). We have the following additional comments and proposed revisions to the package insert (PI), the Instruction for Use (IFU), and Carton Label. Submit a revised PI, IFU, and Carton Label incorporating the changes listed below and those shown in the attached marked up labeling by COB Friday, September 30, 2011. Please note that we may have additional comments as we continue to review the labeling for this application.

For clarity and to distinguish from HFA-propelled inhalation aerosols, the word “CFC-propelled” has been added throughout the PI when describing Combivent Inhalation Aerosol.

Full Prescribing Information Details

1. Section 6.1. Clinical Trials Experience
 - To make the table easier to read and interpret, the adverse reaction data in Table 1 have been rounded to the nearest percent.
2. Section 6.2, Post-Marketing Experience
 - Are Combivent Respimat and Combivent HFA marketed elsewhere in the world and, if so, are there any post-marketing data available yet that should be included to Section 6.2?
3. Sections 8.1 and 13.2, Pregnancy and Animal Toxicology and Pharmacology
 - Per our phone discussion on September 22, 2011, we have changed the wording in Section 8.1 to include the language in Section 13.2. Section 13.2 has been deleted.
4. Section 14, Clinical Studies
 - For Figure 1, the abbreviations CVT R 20/100, IB R 20, and CVTCFC 36/206 are not defined. Expand the abbreviations to describe the products as listed in the label text or consider including a figure legend which explains the abbreviations. You may want to refer to the Ventolin HFA label as an example.

Instructions for Use (IFU)

- Under “Daily Dosing”, for consistency, change names of Figures A and B to Figures 8 and 9, respectively, and change the correlating dosing steps “A” and “B” to “8” and “9”.

Carton Label

- Change the established name to "ipratropium bromide and albuterol" since the 100 mcg strength on the label refers to albuterol base. Then, below "For Oral Inhalation Only" state "Each actuation delivers 120 mcg of albuterol sulfate, equivalent to 100 mcg albuterol, from the mouthpiece”.

Submit your response to me via telephone facsimile to 301-796-9728 or email me at Sadaf.Nabavian@fda.hhs.gov. Your responses will subsequently need to be submitted officially to the NDA.

If you have any questions, please contact Sadaf Nabavian, Regulatory Project Manager at 301-796-2777.

Sadaf Nabavian, Pharm.D.
Regulatory Project Manager

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/s/

SADAF NABAVIAN
09/27/2011



NDA 021747

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road
Ridgefield, Connecticut 06877

ATTENTION: Amy Van Anandel, DVM, MPH
Sr. Associate Director, DRA

Dear Dr. Anandel:

Please refer to your New Drug Application (NDA) dated October 7, 2008, received October 8, 2008, and your April 7, 2011 resubmission, received April 8, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ipratropium Bromide and Albuterol Sulfate Inhalation Spray, 20 mcg/100 mcg.

We also refer to your June 24, 2011, correspondence, received June 27, 2011, requesting review of your proposed proprietary name, Combivent Respimat. We have completed our review of the proposed proprietary name, Combivent Respimat and have concluded that it is acceptable.

The proposed proprietary name, Combivent Respimat, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you. If **any** of the proposed product characteristics as stated in your June 24, 2011, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Nichelle Rashid, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3904. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Sadaf Nabavian, at (301) 796-2777.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
09/22/2011

NDA 21747

Cobmivent Respimat

BI

Please refer to your April 07, 2011, New Drug Application resubmission for Combivent Respimat (albuterol sulfate/ipratropium bromide), and to your amendments dated June 16, and 24, and August 08, 2011. We have the following additional comments and proposed revisions to the package insert (PI) and the Instruction for Use (IFU). Submit a revised PI and IFU incorporating the changes shown in the attached marked up labeling by COB Tuesday, September 13, 2011.

Full Prescribing Information Details

1. Section 6, Adverse Reactions

To be consistent with current safety labeling guidelines, the term adverse reaction is used to refer to untoward effects which occur while receiving a study drug/placebo. Because the determination of possible causality can be subjective, for placebo-controlled clinical trials we have defined an adverse reaction as an untoward event which has occurred more frequently above a certain threshold (generally 1-5%) in patients who receive active drug compared to placebo. In the case of Combivent Respimat, the clinical trials did not contain a placebo group. As such, the operational definition for what constitutes an adverse reaction in the Phase 3 trials are untoward events greater than or equal to 2 percent in the Combivent Respimat treatment group. While this admittedly is a somewhat arbitrary definition of an adverse reaction, it avoids the subjective nature of trying to assess relatedness of a reported adverse event, especially given the lack of a placebo group for comparison.

2. Subsection 6.1, Clinical Trials Experience

- Table 1: We have added several adverse reactions based on review of the non-compressed terms using the definition of an AR as an event that occurred in \geq 2% of patients in the Combivent Respimat treatment group.
- Adverse event descriptions have been deleted and relevant terms have been included as adverse reactions, again, based on the definition as an event that occurred in \geq 2% of patients in the Combivent Respimat treatment group.
- Safety information included for Combivent Inhalation Aerosol should reflect the information presented in the current approved Combivent label. As such, using our working definition of an adverse reaction, several additional terms have been added to this section.

- Table 2 has been deleted and safety information from the long-term safety study is described briefly in the text.
3. Subsection 6.2, Post-Marketing Experience
 - Adverse event descriptions have been deleted and relevant terms have been included as adverse reactions based on the definition as an event that occurred in $\geq 2\%$ of patients in the Combivent Respimat treatment group. In this section, some judgment has been used to omit duplicative terms or obviously unrelated events.
 4. Section 12, Clinical Pharmacology
 - First sentence deleted in Pharmacokinetics section since it only deals with the intrinsic PK characteristic of ipratropium and not the formulation per se or the combination product, Combivent. In addition, the study to support the statement deals with delivery from Respimat using a different product Berodual (fenoterol + ipratropium).
 5. Section 13, Nonclinical Toxicology
 - Deleted Subsection 13.2, Animal Toxicology and Pharmacology, the information is presented in Section 8, Subsection 8.1, Pregnancy.

Patient Labeling

NOTE : Comments (see accompanying IFU document) are based on the original patient instruction for use (IFU) section submitted in your complete response submission dated April 7, 2011. Our comments and edits have been made in order to:

- simplify wording and clarify concepts when possible to ensure that the IFU is consistent with the proposed PI
- remove unnecessary or redundant information
- ensure that the IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

While we acknowledge your submission dated August 8, 2011, with updated IFU in which instructions were made more clear, our comments remain the same and we request that you incorporate them into the updated IFU.

Submit your response to me via telephone facsimile to 301-796-9728 or email at Sadaf.Nabavian@fda.hhs.gov. Your responses will subsequently need to be submitted officially to the NDA.

If you have any questions, please contact Sadaf Nabavian, Regulatory Project Manager at 301-796-2777.

Sadaf Nabavian, Pharm.D.
Regulatory Project Manager

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/s/

SADAF NABAVIAN
09/02/2011



NDA 21-747

**ACKNOWLEDGE –
CLASS 2 RESPONSE**

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

Attention: Amy Van Andel, DVM, MPH
Senior Associate Director, Drug Regulatory Affairs

Dear Dr. Van Andel:

We acknowledge receipt on April 08, 2011, of your April 07, 2011, resubmission of your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Combivent Respimate® (ipratropium bromide and albuterol sulfate) Inhalation Spray.

We consider this a complete, class 2 response to our August 08, 2009, action letter. Therefore, the user fee goal date is October 07, 2011.

If you have any questions, call Sadaf Nabavian, Regulatory Project Manager, at (301) 796-2777.

Sincerely,

{See appended electronic signature page}

Sandy Barnes
Supervisory CSO
Division of Pulmonary, Allergy, and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

SADAF NABAVIAN

04/22/2011

Signed on behalf of Sandy Barnes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Meeting Type: Type C Meeting
Meeting Category: Teleconference
Meeting Date and Time: January 25, 2010
Meeting Location: 3:00-4:00 P.M.
Application Number: NDA 21-747
Product Name: Combivent Respimat
Received Briefing Package December 21, 2009
Sponsor Name: Boehringer Ingelheim
Meeting Requestor: Amy E. Van Andel, DVM, MPH

Meeting Chair: Badrul A. Chowdhury, M.D., Ph.D.
Division Director
Meeting Recorder: Sadaf Nabavian, Pharm.D.
Regulatory Management Officer

Meeting Attendees:

FDA Attendees

Division of Pulmonary and Allergy Products

Badrul A. Chowdhury, M.D., Ph.D., Division Director
Lydia Gilbert-McClain, M.D., Deputy Director
Sally Seymour, M.D., Deputy Director for Safety
Xu Wang, M.D., Ph.D., Clinical Reviewer
Thomas Permutt, Ph.D., Director, Division of Biometrics II
Joan Buenconsejo, Ph.D., Acting Statistical Team Leader
Alan Schroeder, Ph.D., CMC Reviewer, ONDQA
Xu Yun., Ph.D., Acting Clinical Pharmacology Team Leader
Shea Molly, Ph.D., Supervisor for Pharmacology/Toxicology
Martha Nguyen, Regulatory Counsel, Office of Regulatory Policy
Sadaf Nabavian, Pharm.D., Regulatory Management Officer

Sponsor Attendees

Amy Van Andel, Sr. Associate Director, Drug Regulatory Affairs
Jeff Snyder, Executive Director, Drug Regulatory Affairs
Tacy Pack, Director, Drug Regulatory Affairs
Anna Wysowskyj, Sr. Associate Director, Drug Regulatory Affairs
Bihong Lu, Associate Director, Drug Regulatory Affairs

1.0 BACKGROUND

Boehringer Ingelheim submitted a meeting request dated November 17, 2009, for a Type C teleconference meeting to discuss the Division's comments stated in the complete response letter and to clarify process steps and timelines associated with the final approval of Combivent Respimat.

A briefing package for this meeting was submitted on December 21, 2009. Upon review of the briefing package, the Division responded to BI's questions via fax on January 21, 2010. The content of that fax is printed below. BI informed the Division that they would like further clarification on two questions (Question 1 and Question 5). The clarification requests are provided directly under the relevant original responses followed by any discussion that took place at the meeting. BI's questions are in ***bold italics***; FDA's response is in *italics*; BI's clarification requests and any discussion that took place with the FDA are in normal font.

2.0 DISCUSSION

Question 1:

BI would like to confirm with the Division that submission of the 6-month interim data from trial 1012.62 in the Complete Response for review and approval is acceptable. The complete 1-year data would be provided as soon as available, approximately 6 months following the Complete Response submission, for consideration of a labeling update.

Division Response:

The 6-month interim data from the safety and patient acceptance study is acceptable for submission for review in the complete response. Whether the submitted data are acceptable for approval is a review issue.

The 12-month safety data need to be submitted during the NDA review cycle with adequate time for us to review the information prior to taking action.

BI Clarification Request:

Can the Agency provide BI with an estimation of what it considers adequate time to review the 12 month safety data in the context of a 6 month review period and in the context of a 10 month review period?

Discussion:

The Division replied that the resubmission should include the full report of the first 6 months of data from the 12-month safety and patient acceptance study. The data from the remaining 6 months should be submitted at least 4 weeks before the action date in order for the Division to have an overall assessment of the safety data for the entire 12 months prior to taking action. The data from the second 6 months of the study could be submitted as a preliminary report during the NDA review cycle, and a full report of the entire 12 month safety study should be submitted later in a subsequent NDA supplement.

Question 2:

Boehringer Ingelheim would appreciate FDA's clarification on whether BI's arguments for [REDACTED] (b) (4) would, in principal, be considered a complete response to FDA's comment.

Division Response:

Yes, we agree in principle with your approaches, however this will be review issue.

Discussion:

No discussion occurred.

Question 3:

BI would appreciate understanding whether the proposed modeling studies and container closure integrity information in support of [REDACTED] (b) (4) would, in principal, address FDA's request for supporting information.

Division Response:

Yes, we agree in principle with your approaches, however this will be review issue.

Discussion:

No discussion occurred

Question 4:

Combivent Respimat is not an approved product and no previous approved label exist. BI proposes to provide a clean version as a paper document and electronic MS Word and SPL format files, and a marked copy indicating all changes from the draft labeling submitted to the NDA on July 14, 2009 as a paper document and electronic MS Word

and SPL format files. The marked copy will include explanatory annotations as appropriate.

Does the Division agree with this proposal for submission of the draft labeling in the Complete Response?

Division Response:

Yes, we agree.

Discussion:

No discussion occurred

Question 5:

At the time of the proposed filing of the Complete Response, new safety information for Combivent Respimat will be limited to the 6-month interim data from the 1-year safety and patient acceptance study in COPD (1012.62) and a completed proof of concept study in asthma (1012.57). Given that the 1-year safety and patient acceptance study in COPD is primary data for the Complete Response, BI proposes that the completed clinical trial reports for the 2 aforementioned studies, assuming appropriate tables, listings, narrative and case report forms, addresses all of the requirements of CFR 314.50(d)(5)(vi). A separate document of integrated safety information would not be provided.

Does the Division accept this proposal?

Division Response:

Submit safety data from foreign marketing for approved Respimat products. We are primarily interested in adverse event reports related to device performance issues.

BI Clarification Request:

BI accepts the FDA's request to submit safety data from marketed Respimat products. BI proposes to provide the following clinical information in the Complete Response:

- Clinical trial report for study 1012.62, 6 month interim data results
- Clinical trial report for study 1012.57(proof of concept study in asthma)
- Report of post-marketing safety data from marketed Respimat products with a focus on adverse event reports related to the device

As requested in the FDA comment to Question 1 above, BI will submit the clinical trial report for study 1012.62 containing the 12 month data results following the filing of the above information.

Can the Division confirm that this proposal is acceptable?

Discussion:

The Division accepted BI's proposal.

Question 6:

BI proposes to submit the Combivent Respimat Complete Response as a paper submission in CTD format. The CRFs, individual patient data listings and analysis datasets of the 6-month interim data from Trial 1012.62 will be provided electronically.

Does the Division accept this proposal for the format and datasets to be included in the submission?

Division Response:

Yes, the proposal is acceptable.

Discussion:

No discussion occurred.

On a final note, BI asked the Division regarding the Final Rule published timeline. The Division replied that the Final Rule is still in the clearance stage and currently in the Office of Budget and Financing at the White House.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues that required further discussion.

4.0 ACTION ITEMS

No action items were identified during the meeting.

5.0 ATTACHMENTS AND HANDOUTS

No attachments of handouts were presented at the meeting.

If you have any questions, call Sadaf Nabavian, Regulatory Project Manager, at (301) 796-2777.

Drafted by: SNabavian/01.26.2010

Initialed by: LGilbert-McClain/02.19.2010
BACHowdhury/02.22.2010

Finalized by: SNabavian/02.22.2010

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-21747

GI-1

BOEHRINGER
INGELHEIM
PHARMACEUTICA
LS INC

COMBIVENT RESPIMAT

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/s/

SADAF NABAVIAN
02/22/2010

NDA 21-747
Combivent Respimat
Boehringer Ingelheim

Attached are the FDA responses to your questions (in bold italics) in your December 21, 2009, meeting package regarding Combivent Respimat. You have the option of canceling our teleconference scheduled on January 25, 2010, if these answers are clear to you. If you choose to have the teleconference, we will be prepared to clarify any questions you have regarding our responses. However, please note that if there are any major changes to your development plan (based upon our responses herein), we will not be prepared to discuss, nor reach agreement on, such changes at the meeting. Any modifications to the development plan or additional questions for which you would like FDA feedback should be submitted as a new meeting request.

Please let me know as soon as possible if you would like to cancel the teleconference.

Sadaf Nabavian
Regulatory Project Manager
301-796-2777

QUESTIONS and RESPONSES

Question 1:

BI would like to confirm with the Division that submission of the 6-month interim data from trial 1012.62 in the Complete Response for review and approval is acceptable. The complete 1-year data would be provided as soon as available, approximately 6 months following the Complete Response submission, for consideration of a labeling update.

Division Response:

The 6-month interim data from the safety and patient acceptance study is acceptable for submission for review in the complete response. Whether the submitted data are acceptable for approval is a review issue.

The 12-month safety data need to be submitted during the NDA review cycle with adequate time for us to review the information prior to taking action.

Question 2:

Boehringer Ingelheim would appreciate FDA's clarification on whether BI's arguments [REDACTED] (b) (4) [REDACTED] would, in principal, be considered a complete response to FDA's comment.

Division Response:

Yes, we agree in principle with your approach, however this will be a review issue.

Question 3:

BI would appreciate understanding whether the proposed modeling studies and container closure integrity information in support of [REDACTED] (b) (4) [REDACTED] would, in principal, address FDA's request for supporting information.

Division Response:

Yes, we agree in principle with your approach, however this will be a review issue.

Question 4:

Combivent Respimat is not an approved product and no previous approved label exist. BI proposes to provide a clean version as a paper document and electronic MS Word and SPL format files, and a marked copy indicating all changes from the draft labeling

submitted to the NDA on July 14, 2009 as a paper document and electronic MS Word and SPL format files. The marked copy will include explanatory annotations as appropriate.

Does the Division agree with this proposal for submission of the draft labeling in the Complete Response?

Division Response:

Yes, we agree.

Question 5:

At the time of the proposed filing of the Complete Response, new safety information for Combivent Respimat will be limited to the 6-month interim data from the 1-year safety and patient acceptance study in COPD (1012.62) and a completed proof of concept study in asthma (1012.57). Given that the 1-year safety and patient acceptance study in COPD is primary data for the Complete Response, BI proposes that the completed clinical trial reports for the 2 aforementioned studies, assuming appropriate tables, listings, narrative and case report forms, addresses all of the requirements of CFR 314.50(d)(5)(vi). A separate document of integrated safety information would not be provided.

Does the Division accept this proposal?

Division Response:

Submit safety data from foreign marketing for approved Respimat products. We are primarily interested in adverse event reports related to device performance issues.

Question 6:

BI proposes to submit the Combivent Respimat Complete Response as a paper submission in CTD format. The CRFs, individual patient data listings and analysis datasets of the 6-month interim data from Trial 1012.62 will be provided electronically.

Does the Division accept this proposal for the format and datasets to be included in the submission?

Division Response:

Yes, the proposal is acceptable.

NDA 21-747

Drafted by: SNabavian/01.20.2010

Initialed by: SBarnes/01.20.10
ASchroeder/01.21.10
PPeri/01.21.10
XWang/01.20.10
LGilbert-McClain/01.20.10
BACHowdhury/01.21.10

Finalized by: SNabavian/01.21.10

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-21747

GI-1

BOEHRINGER
INGELHEIM
PHARMACEUTICA
LS INC

COMBIVENT RESPIMAT

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/s/

SADAF NABAVIAN
01/21/2010

NDA 21-747
Combivent Respimat

Please refer to your October 07, 2008, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Combivent Respimat. We are reviewing your submission and we have the following recommendations and requests for information.

1. Provide the compilation of site specific individual patient data listings for use as background material in the upcoming clinical investigator inspections for NDA 21-747, Combivent Respimat. The data listings should include the following parameters:
 - Protocol and protocol amendments
 - Blank CRF
 - Blank ICF
 - Primary efficacy endpoint
 - Secondary efficacy endpoint
 - Concomitant medications
 - Adverse events
 - Withdrawals
 - Deaths
 - Serious adverse events
 - Protocol violations/deviations
 - Randomization list for the site
 - Laboratory values (biochemistry, hematology)
 - Pulmonary function testing results

2. The individual patient data listings should be formatted separately for each of the following four investigators, all enrollers in Protocol # 1012.56:
 - Thomas D. Kaelin, Charleston, SC Site #01037
 - Andras Koser, Greenville, SC Site #01085
 - Lon Lynn, Tampa, FL Site #01048
 - Daniel Lorch, Brandon, FL Site#01058

Also, for each parameter listed in the bullets above, the file should contain a listing of each patient enrolled by that investigator with the pertinent data - e.g., "Primary efficacy endpoint" should contain a listing of Patient 1, 2, 3, 4, etc. with the appropriate outcome of the primary efficacy endpoint.

In order to facilitate the review of your NDA submission, we request that you provide a response to this request electronically no later than Wednesday, January 07, 2009. Also submit it in the form of an amendment in triplicate to the NDA. In your cover letter, indicate in bold that the submission is a response to FDA request for information. Forward the submission to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary and Allergy Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If there are any questions, please contact Sadaf Nabavian, Regulatory Project Manager, at (301) 796-2777.

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/s/

Sadaf Nabavian
12/24/2008 09:37:38 AM
CSO

Sadaf Nabavian
12/24/2008 09:38:24 AM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-747

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

Attention: Amy Van Andel, DVM, MPH
Senior Associate Director, Drug Regulatory Affairs

Dear Dr. Van Andel:

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

We also refer to your November 17, 2009, correspondence requesting an End of Review Teleconference to discuss the Division's comments stated in the CR letter and to clarify process steps and timelines associated with the final approval of Combivent Respimat. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type C meeting.

The meeting is scheduled as follows:

Date: January 25, 2010
Time: 3:00 p.m.- 4:00 p.m. EST

Dial-in information: Please provide a dial-in number and passcode

CDER Participants: Badrul A. Chowdhury, M.D., Ph.D., Division Director
(tentative) Lydia Gilbert-McClain, M.D., Deputy Director
Sally Seymour, M.D., Deputy Director for Safety
Xu Wang, M.D., Ph.D., Clinical Reviewer
Alan Schroeder, Ph.D., CMC Reviewer
Prasad Peri, Ph.D., ONDQA, Pharmaceutical Assessment Lead
Luqi Pei, Ph.D., Acting Supervisor for Pharmacology/Toxicology
Qian Li, Ph.D., Statistical Team Leader
Ruthanna Davi, M.S., Statistical Reviewer
Roy Partha, Ph.D., Acting Team Leader for Clinical Pharmacology

Martha Nguyen, Regulatory Counsel, Office of Regulatory Policy
Sadaf Nabaivan, Pharm.D., Regulatory Project Manager

Provide the background information for the meeting (three copies to the application and 12 desk copies to me) at least one month prior to the meeting. If the materials presented in the information package are inadequate to prepare for the meeting or if we do not receive the package by December 28, 2009, we may cancel or reschedule the meeting.

If you have any questions, call Sadaf Nabavian at (301) 796-2777.

Sincerely,

{See appended electronic signature page}

Sadaf Nabavian, Pharm.D.
Regulatory Project Manager
Division of Pulmonary and Allergy Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-21747

GI-1

BOEHRINGER
INGELHEIM
PHARMACEUTICA
LS INC

COMBIVENT RESPIMAT

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/s/

SADAF NABAVIAN
12/03/2009



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Pulmonary and Allergy Products**

Memorandum of Facsimile Correspondence

Date: June 18, 2009

To: Amy Vander Wal, DVM, MPH

Company: Boehringer Ingelheim Pharmaceuticals, Inc.

Fax: 203-791-6262

Phone: 203-798-5452

From: Carol Hill, MS
Regulatory Health Project Manager
Division of Pulmonary and Allergy Products

Subject: NDA 21-747 re: Labeling Comments

of Pages: 31

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If you are not the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you received this document in error, please immediately notify us by telephone at (301) 796-2300 and return it to us at FDA, 10903 New Hampshire Ave, Building 22, DPAP, Silver Spring, MD 20993.

Thank you.
carol.hill@fda.hhs.gov

NDA 21-747
Boehinger Ingelheim Pharmaceuticals, Inc.
Combivent Respimat

Please refer to your submission dated, October 7, 2008, for Combivent Respimat. We are reviewing your submission and we have the following labeling comments and revisions.

The FDA-proposed revisions to your draft labeling for COMBIVENT RESPIMAT have been made using the clean copy of the word version of the label submitted with your NDA. In the revised labeling, FDA insertions are underlined and deletions are strike-out. Be advised that these labeling changes are not the Agency's final recommendations and that additional labeling changes will be forthcoming as the label continues to be reviewed. Comments to explain the FDA edits are provided throughout the package insert where appropriate, and areas where data are needed are indicated with "XXX." Note that the Patient Instructions for Use is not being reviewed at this time. We have the following general comments:

1. Changes have been made throughout the label to comply with the new Physicians Labeling Rule format (PLR). Since COMBIVENT is a combination of a short-acting beta agonist (albuterol) and an anti-cholinergic, the approved package inserts for combination products in PLR format (i.e. SYMBICORT and ADVAIR DISKUS) and short-acting beta₂-agonists in PLR format (i.e. VENTOLIN HFA) were compared, and formatting and language were adapted from these labels for consistency where appropriate.
2. Revise the headings in the Full Prescribing information Table of Contents to comply with the heading changes throughout the labeling

We ask that you submit revised labeling incorporating these changes by close of business on July 8, 2009. If you have any questions, contact Carol Hill, Regulatory Health Project Manager at 301-796-1226.

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

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/s/

Carol F. Hill
6/18/2009 06:12:49 PM
CSO

Carol F. Hill
6/18/2009 06:13:29 PM
CSO

MEMORANDUM OF TELECON

DATE: March 11, 2009

APPLICATION NUMBER: NDA 21-747

BETWEEN:

Name: Jeff Snyder, Executive Director, Drug Regulatory Affairs
Chris Corsico, VP Drug Regulatory Affairs
Amy Van Andel, Sr. Associate Director, Drug Regulatory Affairs
Eben Rubin, Executive Director, Clinical Research, Pulmonary
Chet Wood, Director, Clinical Research, Pulmonary
Mo Ghafouri, Sr. Associate Director, Clinical Research,
Pulmonary
Mary Zhao, Trial Statistician
Anna Wysowskyj, Drug Regulatory Affairs
Bihong Lu, Drug Regulatory Affairs

Phone: 1-866-603-2932 (Access Code (b) (4))

Representing: Boehringer Ingelheim

AND

Name: Badrul A. Chowdhury, M.D., Ph.D., Director, Division of
Pulmonary and Allergy Products
Lydia Gilbert-McClain, M.D., Deputy Director, Division of
Pulmonary and Allergy Products
Xu Wang, M.D., Ph.D., Clinical Reviewer, Division of Pulmonary
and Allergy Products
Sandy Barnes, B.S., Chief Project Management Staff, Division of
Pulmonary and Allergy Products

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

Sadaf Nabavian, Pharm.D., Regulatory Project Manager, Division
of Pulmonary and Allergy Products

SUBJECT: NDA 21-747, Combivent Respimat

Background

The Division requested a teleconference with BI to discuss issues regarding pending NDA 21-747, Combivent Respimat following the Division's mid-cycle review.

Discussion

The Division provided BI with an update on the review of the application and stated that they recognize the importance of the application from the standpoint of patients who are currently on Combivent CFC products and from the standpoint of the Proposed Rule.

The discussion began with the division providing BI with an update on the review of the safety and efficacy of the application. The Division noted that that determination of efficacy for the Combivent Respimat program was the primary focus of the multiple discussions and interactions between BI and the Division for the past several years. The division is sensitive to the challenges that BI had to confront in the development of the Respimat (b)(4). On a positive note, based on our preliminary review, the efficacy data submitted in the NDA appears acceptable. The Division then discussed the safety data in the application. (b)(4)

The Combivent Respimat product is meant to be a replacement product for the currently marketed Combivent CFC, and as such, long term safety data with Combivent Respimat in COPD patients will be necessary for approval. Our current thinking is heavily influenced by our experience with the albuterol CFC to HFA switch. Since the switch, we have received an extensive number of complaints regarding a perceived lack of efficacy and safety of the HFA products, in spite of the extensive amount of controlled clinical data generated for these switch programs. We have been able to respond to these complaints with data from the long term controlled studies that confirmed the efficacy and safety of these products.

The Combivent Respimat application does not contain and long term studies in COPD evaluating the safety of the product, and given the experience with the albuterol switch products, 12 weeks exposure data alone will not be sufficient. The 6-month safety study with ipratropium Respimat is not sufficient to address long term safety because the study does not evaluate safety of Combivent Respimat, and the duration of the study is not sufficient for a product that is intended

for chronic, long-term use. We have typically followed the ICH guidance on long term studies to guide study duration for these types of studies. In addition, the ipratropium Respimat is not an approved product and we will need to have a long-term safety assessment of the to-be-marketed product – i.e. Combivent Respimat. The Division then stated that a one year safety study will be necessary.

The Division briefly discussed the different products already on the market for COPD patients (e.g., ipratropium, albuterol, and various HFA products) and reminded BI that unlike the MDI products where multiple products are available and there is extensive experience with the MDIs there are no products currently on the market that can provide historical data for the Respimat. Respimat is a new platform therefore, long-term, controlled safety data from a clinical trial is very important.

BI asked if data from the German switch or patient acceptance would be useful. The Division stated that the German information would not be useful given that there has been lower consumer acceptance of the HFA products in the US compared to the international sector.

The Proposed Rule for the seven moieties was discussed briefly. The Division informed BI that in the interest of the Public Health, our ultimate goal is to bring good and reliable replacement products onto the market prior to the discontinuation of the CFC products. BI informed the Division that they have [REDACTED] ^{(b) (4)}. BI inquired whether there would be adjustments to the date for the Final Rule given the safety requirements and given the amount of CFC that they have. The Division responded that they cannot make a comment at this time regarding the Final Rule but will take all of the issues raised into consideration.

The following details of the proposed safety study were discussed

1. The long term safety study should include sufficient patients to assess safety. The sample size envisioned is in the “hundreds.”
2. The duration of the study is expected to be one year, however we would consider having 6 months of data included in the resubmission with the additional 6 months of data being submitted as soon as it is available.
3. We would recommend that the study include the following study arms:
 - Combivent Respimat
 - Combivent CFC
 - Albuterol HFA and Ipratropium HFA as separate inhalers given concomitantly

The third arm would provide additional data on patient preference regarding the use of a fixed does combination product compared to the individual products.

4. We would be looking for dropouts due to safety and efficacy, and patient perception and patient acceptance data.

The Division also advised BI to keep in mind that the goal is not to establish efficacy, the expectation is that the drug will continue to be efficacious and the study will provide long term, patient use data safety.

In conclusion, the Division reiterated that the NDA review is ongoing and advised BI to take all of the recommendations conveyed in this telephone conversation very seriously and to consider conducting the additional safety study.

Action Item

BI committed to address the issues raised in today's teleconference after they have discussed them internally.

The Division recommended that BI submit a protocol for review as early as possible.

Sadaf Nabavian, Pharm.D.
Regulatory Project Management Officer

Drafted: SNabavian/03.18.09
Revised Sbarnes 5/27/09

Initialed: Xu Wang -3/20/09
LGilbert-McClain 3/20/09 and 5/28/09
BACHowdhury/

Finalized:

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/s/

Sandra Barnes
5/28/2009 11:45:43 AM
CSO



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

FACSIMILE TRANSMITTAL SHEET

DATE: April 29, 2009

To: Amy E. Van Andel, DVM, MPH Sr. Asso. Dir., Drug Regulatory Affairs	From: Carol Hill, M.S. Regulatory Health Project Manager
Company: Boehringer Ingelheim Pharm.	Division of Pulmonary and Allergy Products
Fax number: 203-791-6262	Fax number: 301-796-9728
Phone number: 203-798-5452	Phone number: 301-796-1226

Subject: NDA 21-747 CMC Information Request III

Total no. of pages including cover: 3

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NDA 21-747
Combivent Respimat

Please refer to your October 7, 2008, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Combivent Respimat. We are reviewing your amendment dated, April 3, 2009, submitted in response to our March 19, 2009, information request. We have the following requests.

1. This pertains to your response to our comment #11b in your amendment dated April 3, 2009. Describe the protocol used for the study which determined the number of delivered doses from the inhaler when cocking the inhaler in various orientations. Provide the data generated in this study and include graphical data for orientations other than 180 degrees (inverted).
2. This pertains to section 4.11.5 of the Pharmaceutical Development Report of the original NDA (as referenced in your amendment dated April 3, 2009: Response 12). Provide any additional available information pertaining to Complaint #77/2003 (pertaining to the damaged plastic cap of the cartridge with a burst shaft immersing into the inhalation solution) and evaluate whether this damage is possible to replicate during insertion of the cartridge into the inhaler. If so, consider possible strategies to remedy this problem.
3. This pertains to your response to our comment #13d in your amendment dated April 3, 2009. Modify your agreement to provide the updated specification documents (including methods) as a correspondence, as soon as they are available, rather than waiting for the NDA annual report.

If you have any questions, contact Carol Hill, Regulatory Health Project Manager at 301-796-1226.

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/s/

Carol F. Hill
4/29/2009 04:25:09 PM
CSO

Document Information Page

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FACSIMILE TRANSMITTAL SHEET

DATE: March 19, 2009

To: Amy Van Andel, DVM, MPH Senior Associate Director	From: LCDR Sadaf Nabaivan Regulatory Project Manager
Company: BI	Division of Pulmonary and Allergy Products
Fax number: 203-791-6262	Fax number: 301-796-9718
Phone number: 203-798-5452	Phone number: 301-796-2777
Subject: NDA 21-747 CMC Information Request	

Total no. of pages including cover: 5

Comments: Please acknowledge receipt.

Document to be mailed: YES NO

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NDA 21-747
Combivent Respimat

Please refer to your October 07, 2008, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Combivent Respimat. We are reviewing your submission and we have the following requests for information.

1. Provide an updated letter of authorization (LOA) for DMF (b) (4). The LOA dated September 5, 2008 and provided in the DMF with a copy in your NDA, does not contain a DMF number.
2. Clarify how you periodically requalify the Andersen Cascade Impactor and how you qualify a new Andersen Cascade Impactor.
3. This pertains to your extractables and leachables report #U07-2274 in Module 3, volume 1 of your NDA. Please refer to your Tables 8 and 9. Clarify the extractables category of (b) (4) which is present at levels much higher than the sum of all other identified extractables combined. State whether the (b) (4) and what is the supporting evidence for this assignment.
4. This pertains to your specification for Aerodynamic Particle Size Distribution – Laser Diffraction. Explain the reason for collecting (and averaging) data from four individual actuations at the beginning and four individual actuations at the end of the inhaler's life.
5. Clarify the differences between (b) (4) presentations of the drug product.
6. This pertains to your drug product specifications for Aerodynamic Particle Size Distribution – Andersen Cascade Impactor. Reconsider the proposed acceptance criteria for Group 1b, which seem excessively broad, based upon your data, (b) (4).
7. This pertains to your drug product specifications for Aerodynamic Particle Size Distribution – Laser Diffraction. Add acceptance criteria for mean results for the groups of the APSD-LD specification.
8. Provide data to demonstrate the stability of the drug product at the pH extremes ((b) (4) permitted by the proposed drug product specification.
9. Provide data to demonstrate the stability of the active ingredients in the drug product (before use and while in use) at the minimum concentration of disodium edetate permitted by the drug product specification ((b) (4)l).

10. Clarify what is the cause of the following observed situation in the supporting stability study: a particular drug product unit which required significantly more variable priming actuations (e.g. 10 variable priming actuations).
11. The following comments pertain to page 71 of your Document Number H 008810, regarding the in-use testing of the drug product (Module 3, volume 9).
 - a. This pertains to two low doses delivered by drug product units which were attributed to a (b) (4). Provide clarification as to how this manufacturing defect occurred and how the in-process controls have been changed to prevent the reoccurrence of this problem.
 - b. This pertains to two low doses delivered which were attributed to the inhalers not being cocked correctly in an upright (vertical) position as required by the instructions for use. Provide “worst case” data demonstrating the consequences of improper use, e.g., when the inhaler is held in various orientations other than vertical while the inhaler is cocked, and the consequences if this improper use is continued over the life of the inhaler.
 - c. This pertains to a very low delivered dose which was attributed to a malfunctioning (b) (4). Provide clarification as to how this manufacturing defect occurred and how the in-process controls have been modified to prevent reoccurrence of this problem.
12. Provide information about the numbers of Respimat A4 and A5 devices that have failed to perform properly in all clinical and stability studies, along with a brief summary of the results of your investigations.
13. Provide post-approval agreements as listed below, (b) (4)
[REDACTED]
 - a. To reevaluate the drug product specifications (acceptance criteria) as more release and stability data pertaining to commercial batches is obtained from at least 10 commercial batches for the U.S. Market.
 - b. To collect data from both Aerodynamic Particle Size Distribution methods, employing the Andersen Cascade Impactor and the Laser Diffraction methods in addition to collecting data pertaining to the remainder of the specifications.
 - c. To inform the FDA about each “quality relevant change” of the analytical procedure for aerodynamic particle size distribution (APSD-LD) including the instrument, instrumental attachments, software and procedure in a supplemental application consistent with the requirements of 21 CFR 314.70; to evaluate each change “by a risk analysis as part of BI’s internal

changes control procedure to verify the influence of the change on the analytical determination;" to confirm "all quality relevant changes by revalidation and depending on the change, supported by comparative data."

- d. To incorporate into the applicable documents (e.g., the specification documents) the drug product specification and method changes agreed to during the course of the NDA review. No other changes besides those listed by BI will be incorporated. Provide a list of the agreed upon changes and provide the documents as soon as they are available.

14. You are also reminded of the following post-approval agreements (b) (4)

[REDACTED]

- a. to revisit the extractable specifications for the Respimat (device) components after 1 year (estimated 10 inhaler batches);
- b. to revisit the extractable specifications for the cartridge container components after 1 year (approximately 10 container and cap batches);

In order to facilitate the review of your NDA submission, we request that you provide a response to the information requests no later than April 03, 2009. Also submit it in the form of an amendment in triplicate to the NDA. In your cover letter, indicate in bold that the submission is a response to FDA request for information. Forward the submission to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary and Allergy Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If there are any questions, please contact Sadaf Nabavian, Regulatory Project Manager, at (301) 796-2777.

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/s/

Sadaf Nabavian
3/19/2009 02:58:26 PM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-747

Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Rd.
Ridgefield, CT 06877

ATTENTION: Amy Van Anandel, DVM, MPH
Senior Associate Director, Drug Regulatory Affairs

Dear Dr. Van Anandel:

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

We also refer to your November 7, 2008, correspondence, received November 10, 2008, requesting review of your proposed proprietary name, Combivent Respimat. We have completed our review of Combivent Respimat and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your November 7, 2009, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Sean Bradley, R.Ph., Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-1332. For any other information regarding this application contact Ms. Sadaf Nabavian, Regulatory Project Manager, at 301-796-2777.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, MD, Ph.D.
Director
Division of Pulmonary and Allergy Products
Office of Drug Evaluation
Center for Drug Evaluation and Research

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/s/

Badrul Chowdhury
2/27/2009 10:52:19 AM

Document Information Page

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FACSIMILE TRANSMITTAL SHEET

DATE: February 04, 2009

To: Amy Van Andel, DVM, MPH Senior Associate Director	From: LCDR Sadaf Nabaivan Regulatory Project Manager
Company: BI	Division of Pulmonary and Allergy Products
Fax number: 203-791-6262	Fax number: 301-796-9718
Phone number: 203-798-5452	Phone number: 301-796-2777
Subject: NDA 21-747 Information Request	

Total no. of pages including cover: 3

Comments: Please acknowledge receipt.

Document to be mailed: YES NO

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NDA 21-747
Combivent Respimat

Please refer to your October 07, 2008, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Combivent Respimat. We are reviewing your submission and we have the following requests for information.

1. Clarify the reasons that (b) (4) the delivered dose of Combivent Respimat given as 11.4 µL per actuation from the same Respimat device design.
2. Clarify the reasons for increased variability in pump delivery (b) (4)
3. Comment on the observation that both the delivered dose and the pump delivery data in Table 33, the fine particle fraction data in Table 34 and the APSD stage grouping data in Table 35 (Section P2) appear to show greater variability for inhalers returned from the clinic than for inhalers tested at batch release.
4. Provide the weight of (b) (4), so that the detection limit of (b) (4) may be assessed.
5. Indicate the amount of the (b) (4)
6. Provide a detailed list of differences, if any, between the routine extractables testing for (b) (4) Combivent Respimat.
7. Provide a detailed list of differences, if any, between the information provided in Report U07-2275-02 and in the overall NDA 21-747 (pertaining to extractables and leachables of the Respimat inhaler for Combivent Respimat's device components) (b) (4)
8. Provide data to justify the (b) (4) holding period for the bulk solution formulation prior to the end of filling. Describe the materials that comprise the part of the storage vessel for the bulk solution which contacts the solution formulation.
9. Clarify how you control the activity of the benzalkonium chloride excipient from different manufacturers, or alternatively, specify the manufacturer used in development and use the same source for the commercial product.
10. Clarify the acceptance testing that you perform when receiving each batch of each excipient.
11. Provide representative certificates of analysis for each excipient.
12. Provide the analytical procedures from the specifications for "(b) (4) hydrochloric acid" if they differ from the NF monograph.
13. Provide a brief summary of the preparation and characterization of the (b) (4) internal standard (b) (4) used in Method 029126-D3.

14. In the validation report (#ADD 1410 of Module 3, volume 3) for the method for various degradation products (method #029125-03), explain the footnote provided in a number of tables (e.g., Footnote 1, Table 93, page 93) which states the following: “resolution below (b) (4), but the selectivity was still given.”
15. Clarify in the methods for APSD/laser diffraction how the (b) (4) and indicate how a single result is obtained from all of the data over the course of the run.
16. This pertains to your batch analyses for the drug product (Section 3.2.P.5.4.). Clarify where the method is described for leachables, as well as any validation data for the method, and state the limits of quantification for the various specified leachables.
17. We recommend annual and expiry testing for sterility testing on stability. (b) (4)
18. This pertains to information on page 38 of your Report U07-2290 in volume 5 of Module 3 of the NDA (pertaining to the justification of specifications for the drug product: solution parameters). This refers to the HPLC-MS method as having number 027238-01 for determination of SCH 1100 BR. The specification sheet for this method and the HPLC-MS method, however, identify it as number 029126-03. Please resolve this discrepancy.
19. Provide a summary of comparative data for the ion chromatography method previously employed for SCH 1100 BR and the HPLC-MS method for SCH 1100 BR.

In order to facilitate the review of your NDA submission, we request that you provide a response to the information requests no later than Monday, February 23, 2009. Also submit it in the form of an amendment in triplicate to the NDA. In your cover letter, indicate in bold that the submission is a response to FDA request for information. Forward the submission to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary and Allergy Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If there are any questions, please contact Sadaf Nabavian, Regulatory Project Manager, at (301) 796-2777.

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/s/

Sadaf Nabavian
2/4/2009 02:41:31 PM
CSO



FILING COMMUNICATION

NDA 21-747

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

Attention: Amy Van Andel, DVM, MPH
Senior Associate Director, Drug Regulatory Affairs

Dear Dr. Van Andel:

Please refer to your new drug application (NDA) dated October 07, 2008, received October 08, 2008, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Combivent Respimat (ipratropium bromide and albuterol sulfate) Inhalation Spray.

We also refer to your submissions dated October 15, and, November 06, 07, 11, 13, and 14, 2008.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is Standard. Therefore, the User Fee Goal Date is August 08, 2009.

In addition, during our filing review of your application we note that information is needed with respect to the chemistry, manufacturing, and control information provided. Below are our comments and requests for information.

1. As requested in the End of Phase 2(EOP2) meeting dated January 18, 2008, provide in vitro comparative data (ASPD and Delivered Dose) for the Respimat device containing the ipratropium bromide and albuterol sulfate combination formulation compared to albuterol sulfate single ingredient delivered by the Respimat device. We note that you have provided these data for ipratropium bromide in the pharmaceutical development report of Module 3 but not for albuterol sulfate.
2. Update the NDA with in-use stability with drug product stored at 21 months followed by insertion of the cartridge into the Respimat device.

3. As requested in the EOP2 meeting, provide a characterization study to demonstrate the presence or absence of foreign particulates in the drug product.
4. This pertains to your document number: U07-2275-02 in volume 1 of module 3. This report provides information about extractables and leachables of the Respimat inhaler. (b) (4)

We also have the following labeling comments regarding conformance of your proposed labeling with the Physician Labeling Rule (PLR) format requirements. Submit revised labeling incorporating the following comments:

General Comments

5. 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).
6. Refer to <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for fictitious examples of labeling format.

Highlights

7. 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

8. 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

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

Use in Specific Populations:

10. This section should be included proceeding 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

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

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

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

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

If you have any questions, call Sadaf Nabavian, Regulatory Project Manager, at (301) 796-2777.

Sincerely,

{See appended electronic signature page}

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

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/s/

Badrul Chowdhury
12/16/2008 12:13:34 PM



NDA 21-747

NDA ACKNOWLEDGMENT

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

Attention: Amy Van Andel, DVM, MPH
Senior Associate Director, Drug Regulatory Affairs

Dear Dr. Van Andel:

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

Name of Drug Product:	Combivent® Respimat®
Date of Application:	October 07, 2008
Date of Receipt:	October 08, 2008
Review Priority Classification:	Standard
Our Reference Number:	NDA 21-747

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on December 05, 2008, in accordance with 21 CFR 314.101(a).

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary and Allergy Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

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If you have any questions, call Sadaf Nabavian, Regulatory Project Manager, at (301) 796-2777.

Sincerely,

{See appended electronic signature page}

Sadaf Nabavian, Pharm.D.
Regulatory Health Project Manager
Division of Pulmonary and Allergy Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Sadaf Nabavian
10/23/2008 11:34:39 AM



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

FACSIMILE TRANSMITTAL SHEET

DATE: January 31, 2008

To: Dr. John Calhoun Manager, Drug Regulatory Affairs	From: LCDR Sadaf Nabavian Regulatory Project Manager
Company: Boehringer Ingelheim Pharmaceuticals, Inc.	Division of Pulmonary and Allergy Products
Fax number: 203-791-6262	Fax number: 301-796-9718
Phone number: 203-791-6877	Phone number: 301-796-2777

Subject: IND 57,948/Final Meeting Minutes

Total no. of pages including cover: 12

Comments: (include cover page)

Please confirm receipt

Document to be mailed: YES xNO

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FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Meeting Type: Type B Meeting
Meeting Category: Teleconference
Meeting Date and Time: January 16, 2008
Meeting Location: 10:30-11:30 P.M.
Application Number: IND 57,948
Product Name: Combivent Respimat
Received Briefing Package December 19, 2007
Sponsor Name: Boehringer Ingelheim
Meeting Requestor: John Calhoun, Ph.D.
Manager, Drug Regulatory Affairs
Meeting Chair: Badrul A. Chowdhury, M.D., Ph.D.
Division Director
Meeting Recorder: Sadaf Nabavian, Pharm.D.
Regulatory Management Officer
Meeting Attendees:

FDA Attendees

Division of Pulmonary and Allergy Products

Badrul A. Chowdhury, M.D., Ph.D., Division Director
Sally Seymour, M.D., Clinical Team Leader
Anthony Durmowicz, M.D., Clinical Reviewer
Prasad Peri, Ph.D., Pharmaceutical Assessment Leader
Ted Guo, Ph.D., Statistical Reviewer
Sadaf Nabavian, Pharm.D., Regulatory Management Officer

Sponsor Attendees

Boehringer Ingelheim

John Calhoun, Ph.D., Manager, Drug Regulatory Affairs
Jeff Snyder, Executive Director, Drug Regulatory Affairs
Amy Van Andel, D.V.M., M.P.H., Senior Associate, Director Drug Regulatory Affairs
Walter Robak, Senior Associate Director, Technical Drug Regulatory Affairs
Mo Ghafouri, Ph.D., Senior Associate Director, Respiratory Clinical Research

1.0 BACKGROUND

Boehringer Ingelheim submitted a meeting request dated November 14, 2007, for a Type B, Pre-NDA meeting to obtain agreement with the Division on the content and format of the Combivent Respimat NDA.

A briefing package for this meeting was submitted on December 14, 2007. Upon review of the briefing package, the Division responded to Boehringer Ingeleheim questions via fax on January 10, 2008. Boehringer Ingeleheim requested the face to face meeting to be changed to a teleconference and informed the Division that they would like further clarification on the following questions: Q4.Section 13.1 and Appendix 7, Q7.Section 12.5, Q1.Section 11 and under Additional Comments bullet 4 regarding CMC comments.

The content of that fax is printed below. Any discussion that took place at the meeting is captured directly under the relevant original response including any changes in our original position. Boehringer Ingelheim's questions are in ***bold italics***; FDA's response is in *italics*; discussion is in normal font.

QUESTION and RESPONSE

Question 1. Section 13.1:

BI is proposing to submit the COMBIVENT RESPIMAT NDA as a paper submission in CTD format. The datasets/listings, labeling and CRFs will be provided electronically. Does the Division concur with this proposal?

FDA Response:

Yes, your proposal is acceptable.

Discussion:

The sponsor accepted FDA's response, no discussion occurred.

Question 2. Section 13.1:

Centralized digital ECGs were collected for the 1012.46 trial. The ECGs were reviewed and analyzed by (b) (4), and it was concluded that there was no evidence of any clinically relevant changes in ECG. A summary report from (b) (4) will be included in the NDA. During the first pre-NDA meeting for COMBIVENT RESPIMAT with the Division in September 2003 it was agreed to have the digital ECG data available upon request. We do not propose to load the ECG data from the 1012.46 trial into the ECG warehouse but will make the data available to Division upon request. Does the Division concur with this proposal?

FDA Response:

Yes, we concur that the digital ECG data will be made available to the Division upon request.

Discussion:

The sponsor accepted FDA's response, no discussion occurred.

Question 3. Section 13.1:

Analysis datasets will be provided only for the pivotal studies 1012.46 and 1012.56. Does the Division agree with this proposal? If yes, does the Division agree that this will be sufficient for the NDA?

FDA Response:

We agree. However, data sets from other supportive studies should be made available upon request.

Discussion:

The sponsor accepted FDA's response, no discussion occurred.

Question 4. Section 13.1 and Appendix 7:

Does the Division concur with the proposed structure and format of the tabulation and analysis datasets?

FDA Response:

We do not see problems at this stage (we might need clarification later during review). In addition, provide computer codes used to create derived variables.

Discussion:

The Division clarified for BI that the only intent of the response was to ensure the computer codes were provided and for BI to explain how the derived variables are calculated by providing relevant computer programs or mathematical formulas. BI agreed to provide the data.

Question 1. Section 12.1.2:

Does the Division agree that the proposed labeling is supported by the COMBIVENT RESPIMAT clinical program?

FDA Response:

The contents of the proposed label will be a review issue.

Discussion:

The sponsor accepted FDA's response, no discussion occurred.

Question 2. Section 12.2.3 and Appendix 5:

The COMBIVENT RESPIMAT NDA will be supported by a single pivotal study (Trial 1012.56) with supportive information from a single additional study (Trial 1012.46). Other supportive studies included in the NDA were performed with the individual components of COMBIVENT RESPIMAT. Given that the NDA will contain a single pivotal study with one supportive efficacy study, we propose that the SCE and

supportive tables, figures, and listings address all content requirements per 21 CFR 314.50(d)(5)(v), including meeting the requirements for the Integrated Summary of Effectiveness Data. Does the Division concur with this proposal?

FDA Response:

Yes, we concur.

Discussion:

The sponsor accepted FDA's response, no discussion occurred.

Question 3. Section 12.2.3:

There are distinct methodological differences between trials 1012.46 and 1012.56 including dose, method of blinding, inclusion of placebo, and statistical analysis plan. We believe that due to these differences, the integration of efficacy data across these 2 studies is scientifically invalid. Therefore, the NDA will not contain any integrated displays containing efficacy data from these two studies side by side. Does the Division agree with the proposal that the SCE describe and analyze each study individually?

FDA Response:

Yes, your proposal is acceptable.

Discussion:

The sponsor accepted FDA's response, no discussion occurred.

Question 4. Section 12.3.1 and Appendix 6:

The COMBIVENT RESPIMAT NDA will be supported by a single pivotal study, 1012.56, with additional information from study 1012.46 conducted with a different dose. We propose that the SCS and supportive tables, figures, and listings address all content requirements per 21 CFR 314.50(d)(5)(vi), including meeting the requirements for the Integrated Summary of Safety Data. Does the Division concur with this proposal?

FDA Response:

Yes, your proposal is acceptable.

Discussion:

The sponsor accepted FDA's response, no discussion occurred.

Question 5. Section 12.3.3:

Upon the completion of the 1012.56 trial there will be no ongoing studies of COMBIVENT RESPIMAT, and therefore no additional data from clinical studies with COMBIVENT RESPIMAT could be included in the four-month safety update. Therefore, does the Division agree that a four-month safety update is not required for the COMBIVENT RESPIMAT NDA?

FDA Response:

Yes, your proposal is acceptable.

Discussion:

The sponsor accepted FDA's response, no discussion occurred.

Question 6. Section 12.4:

Does FDA agree that the information proposed to support ipratropium RESPIMAT as a drug and device comparator in the NDA will be adequate to bridge ipratropium RESPIMAT to ipratropium CFC and confirm the combination rationale for COMBIVENT RESPIMAT?

FDA Response:

The information proposed may be adequate but will be a review issue.

Discussion:

The sponsor accepted FDA's response, no discussion occurred.

Question 7. Section 12.5:

In line with Guidance ICH E3 and ICH M4, narratives will only be provided for deaths and other serious adverse events in the NDA and they will be located within the respective clinical trial reports located in Module 5. Is this approach acceptable to the Division?

FDA Response:

We do not agree. Also include narratives for patients who withdraw due to adverse events.

Discussion:

BI inquired if it would be acceptable to include the narratives for patients who withdrew due to adverse events from Study 1012.46 and Study 1012.56 only. The Division stated that was acceptable. BI asked if the additional narratives for Study 1012.46 could be submitted in Module 2 separately from the study report. The Division stated that was acceptable as long as the narratives were titled appropriately and easily accessible.

Question 1. Section 11 (Chemistry, Manufacturing and Controls):

Does the FDA agree that Combivent Respimat NDA does not need to contain a drug substance “S” section since all CMC information is referenced to BI Type II Drug Master Files (DMF) for ipratropium bromide and albuterol sulfate?

FDA Response:

We do not agree.

- *Provide reference to letters of authorization to the DMFs in the S section.*
- *Provide the current specifications for the two drug substances in the “S” section of the NDA.*

Discussion:

In response to the above stated question, the Division stated that by providing the reference and specifications in the “S” section it’s only for an ease of the review when submitting the NDA. BI responded that they will consider our recommendations.

Question 2. Section 3.2.P.3.3 (Description of manufacturing process and process controls):

Does the FDA agree with BI’s proposal that the detailed narrative description of the method of manufacture (in conformance with 21 CFR 314.50(d)(1)(ii)(c) will be the regulatory document maintained throughout the life of the NDA?

FDA Response:

Yes, we agree.

Discussion:

The sponsor accepted FDA’s response, no discussion occurred.

Question 3. Section 3.2.P.8 (Stability):

Does the FDA agree with BI’s proposal to:

- *Optionally submit the NDA with 6 months of accelerated (40°C/75% RH) and 9 months of long term (26°C/60% RH) stability data from the primary stability batches and,*
- *Amend the NDA with 12 months long term (25°C/60 % RH) stability data approximately 2 months after the NDA submission without stopping or extending the review clock?*

FDA Response:

Yes, we agree. The shelf life will be dependent on the robustness of the long term data.

Discussion:

The sponsor accepted FDA's response, no discussion occurred.

Question 4. Section 3.2.P.8 (Stability):

Does the FDA agree with the primary and supportive stability dataset of the NDA?

FDA Response:

Yes, we agree.

Discussion:

The sponsor accepted FDA's response, no discussion occurred.

Question 5. Section 3.3.R.1 (Executed batch records):

Does the FDA agree with the proposal to submit two executed batch records for the primary stability batches manufactured to the minimum and maximum production batch size?

FDA Response:

We recommend submitting 3 batch records. If the issue is with submitting paper copies, we will accept electronic documents (eCTD) if available as appropriate.

Additional Comments:

Clinical:

- Regarding BI's plan to submit an NDA with one "pivotal" clinical trial to support the efficacy of Combivent Respimat, as discussed at a meeting on December 21, 2005, and reiterated at the End Of Phase 2 meeting on April 26, 2006, the Division does have reservations regarding your plan to perform a single "pivotal" clinical trial especially since previous studies have failed to demonstrate that the combination is superior to each of its components. However, if efficacy findings are robust, a single trial may be sufficient to establish efficacy.

Chemistry, Manufacturing and Control (CMC):

- We note that the proposed acceptance criteria for impurities/degradant products for the drug product are higher than the normal. Note that all impurities/related substances in the drug product will need to be specified, identified or qualified as per ICH Q3B(R). Special considerations apply to impurities that are deemed structural alerts.
- Provide results for Anderson Cascade Impactor aerodynamic particle size distribution (APSD) and emitted dose from *in vitro* studies for the individual components of the Combivent Respimat drug product and the APSD and emitted dose results of the individual component ipratropium bromide delivered through the Respimat device.
- Include a well documented Pharmaceutical Development Report as per ICH-Q8 guideline and highlight how critical quality attributes and critical process parameters are identified and controlled.
- At the beginning of the CMC section, include a table of all facilities, include specifically what is the function of each facility, the point of contact and address, the CFN number, and the complete name and address of the facility.
- Ensure that all of the listed facilities are ready for inspection by the day the application is submitted, and include a statement confirming to this in the NDA cover letter.
- Provide tabular summaries of your stability data, organized by test parameter, and separated by manufacturing site, batch, storage condition and container closure system. Provide graphical summaries of any trending stability data, organized by test parameter, including mean and individual data.

Discussion:

In regards to the second bullet under the CMC section, the Division alerted BI to the importance in providing these results for APSD since it will be a critical point for review when submitting the NDA. (b) (4)

BI asked the Division for an update on the status of the Proposed Rule and requested the Division's feedback on an estimated time before the essential use designation for the currently marketed Combivent MDI is removed. The Division responded that they don't have a specific time frame or outcome on the Final Ruling at this time. Currently the public comments, including those made by BI are being addressed, however no specific time can be determined since other branches of the US Government are also involved in the process. The Division commented that they would like to have the rule finalized as soon as possible and receive support by the other branches of the government.

BI asked if the Division had any idea if there will be any chance of the extension of the dates proposed for removal of essential use designations for BI's product. The Division responded that the Rule involves 7 moieties, and the proposed rule leaves open the possibility of having different dates for the different moieties. The Division does not have any further comment on extension of timelines.

The Division asked BI in what time frame they're planning to submit the NDA. BI replied September 12, 2008. The Division inquired that since there's no data from Phase 3 studies at this time, and if it is BI's intention to submit the NDA even if the results of the study are not as expected. BI indicated that if the results of the Phase 3 study are not as expected, they will be in contact with the Division. For this meeting, BI accelerated their internal timelines to receive feedback from the Division on the structure and format necessary to proceed in submitting the NDA. The Division noted that typically a PreNDA meeting includes results of the Phase 3 program for the Division to provide feedback regarding the adequacy of the data. The Division elaborated that the PreNDA meeting held today is the official meeting prior to the NDA submission and the Division cannot guarantee that a future meeting will be granted prior to the NDA submission if requested by BI. BI understood the Division's concern that having this PreNDA meeting without any data is perhaps premature and not very useful. The Division also inquired if the single study fails, does BI have an alternative plan, (b) (4) BI replied that they are in the process of defining what they would do if the Combivent Respimat data was not as expected, (b) (4), and will share it with the Division at a later date. The Division expressed concern that given the sensitive nature of the Montreal Protocol issues around the continued use of CFC and developing CFC free alternate product, BI is solely relying on one phase 3 study for this product, particularly when a product in the same device with different amounts of active moieties have failed.

In regards to the 4th bullet under Additional Comments, BI agreed to attach the table requested to the 356(h) form. The CMC team stated that BI should ensure that the information is consistent with the information provided in Module 3.

If you have any questions, call Sadaf Nabavian, Regulatory Project Manager, at (301) 796-2777.

Drafted: SNabavian/01.17.2008

Initialed: PPeri/01.31.2008
AAHakim/01.31.2008
TGuo/01.22.2008
QLi/01.22.08
TDurmowicz/01.18.2008
SSeymour/01.18.2008
BAChowdhury/01.31.2008

Finalized: SNabavian/01.31.2008

15 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

Linked Applications

Sponsor Name

Drug Name

IND 57948

BOEHRINGER
INGELHEIM
PHARMACEUTICALS
INC

COMBIVENT RESPIMAT(ALBUTEROL
SULFATE/IPR

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/s/

BADRUL A CHOWDHURY

02/01/2008



IND 57,948

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Walter J. Robak, Senior Associate Director
Technical Drug Regulatory Affairs
900 Ridgebury Road
PO Box 368
Ridgefield, CT 06877

Dear Mr. Robak:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Combivent Respimat (ipratropium bromide & albuterol sulfate) inhalation spray.

We also refer to the meeting between representatives of your firm and the FDA on February 6, 2007. The purpose of the meeting was to discuss the Chemistry, Manufacturing and Controls (CMC) issues associated with the development studies, including the primary stability studies planned for a modified formulation of the Combivent[®] Respimat[®] used in the current Phase III clinical study.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Scott N. Goldie, Ph.D., Regulatory Health Project Manager for Quality at (301) 796-2055.

Sincerely,

{See appended electronic signature page}

Blair Fraser, Ph.D.
Division Director
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF NEW DRUG QUALITY ASSESSMENT

Sponsor Name:	Boehringer Ingelheim Pharmaceuticals, Inc.
Application Number:	IND 57,948
Product Name:	Combivent® Respimat® (ipratropium bromide & albuterol sulfate inhalation spray)
Meeting Type:	Type B
Meeting Category:	End of Phase 2 CMC
Meeting Date and Time:	February 6, 2007 1:00 PM – 2:00 PM EST
Meeting Location:	Food and Drug Administration, White Oak Campus, Silver Spring, MD
Received Briefing Package	December 21, 2006
Meeting Chair	Prasad Peri, Ph.D.
Meeting Recorder	Scott N. Goldie, Ph.D

FDA ATTENDEES:

Office of New Drug Quality Assessment, Division of Pre-Marketing Assessment I

Prasad Peri, Ph.D.; Pharmaceutical Assessment Lead
Alan Schroeder Ph.D.; Review Chemist
Scott N. Goldie, Ph.D., Regulatory Health Project Manager for Quality

Office of New Drugs, Division of Pulmonary and Allergy Products

Sally Seymour, MD; Medical Team Leader
Anthony Durmowicz, MD; Medical Officer

Office of Pharmaceutical Science, Microbiology Staff

John Metcalfe, Ph.D.; Microbiologist

EXTERNAL ATTENDEES:

Christoph Hallmann, MD; International Project Team Leader (Germany)

Bettina Berner, Ph.D.; Technical Drug Regulatory Affairs (Germany)

(b) (4) Consultant (Germany)

Rainer Weitzel, Ph.D.; Drug Delivery Department (Germany)

Volker Lessenich-Henkys, Ph.D.; Production Ingelheim (Germany)

Walter Robak; Technical Drug Regulatory Affairs (US)

Jeff Snyder; Drug Regulatory Affairs (US)

1.0 BACKGROUND

Boehringer Ingelheim Pharmaceuticals (BI) has submitted IND 57,948 for Combivent® Respimat® (ipratropium bromide & albuterol sulfate inhalation spray) proposed for the treatment of chronic obstructive pulmonary disease. Walter J. Robak Jr., Sr. Associate Director, Technical DRA for BI requested a Type B End of Phase 2 CMC meeting on November 21, 2006, received November 22, 2006. The meeting objectives were to discuss the development studies, the proposed control strategy for the proposed commercial drug product, the qualification strategy for a new manufacturing (b) (4) site of packaging components, and BI's proposal for the introduction of physician samples. The meeting request contained sufficient information on discussion topics and questions to determine the applicability of the meeting. The meeting was granted on December 6, 2006. The corresponding briefing package that provided additional information regarding discussion topics and questions was submitted on December 20, 2006, received December 21, 2006. The archived preliminary responses were shared with BI on January 31, 2007, via email to Walter Robak to promote a collaborative and successful discussion at the meeting. On February 2, 2007, FDA requested and received on February 5, 2007, a revised agenda focusing the discussion to any remaining topics that required clarification at the face-to-face meeting. The clarifications received from BI and the meeting discussions from the meeting on February 6, 2007, are captured below:

2.0 DISCUSSION

2.1 Briefing Package Question 1: Does FDA concur with the development plan to qualify a second contract manufacturer for (b) (4)?

FDA Preliminary Response: The proposed plan for qualification of a second contract manufacturer for (b) (4) is adequate from the standpoint of microbiological product quality.

BI's Clarification Request of FDA's Preliminary Response: Based on FDA's response, it is BI's intention to source the material for the three primary stability batches from both (b) (4) sites.

In addition, we would like to get clarification on the term “microbiological product quality”, whether this is a general or specific agreement to our proposal. If the term is specific, we seek clarification on the general terms of the proposal that may not be covered.

Meeting Discussion: FDA reiterated the opinion that the proposal as described in the meeting background package is reasonable. FDA stated that “microbiological product quality” referred to general terms and did not intend to imply specific requirements.

2.2 Briefing Package Question 2: Does FDA agree with BI’s Proposal to:

- Accept the performance characterization studies of the higher concentration of Combivent® Respimat® Inhalation Spray (b) (4) ipratropium bromide/albuterol, corresponding to 40/200 µg/dose), in combination with
- Presented crossover comparison data of the delivered dose and aerodynamic particle size distribution from the higher and lower concentration products.

FDA Preliminary Response: Additional information will need to be evaluated in order to answer this question. We recommend that you include the following information in future submissions.

- a. Provide scientific evidence that demonstrates comparable performance between the Respimat A4 device version and the Respimat A5 device version for an adequate number of devices, using the proposed Combivent formulation.

BI’s Clarification Request of FDA’s Preliminary Response: The Respimat® A4 device is no longer available and has been replaced by the Respimat® A5 device. (b) (4)

(b) (4) which has no impact on the product performance.

Meeting Discussion: FDA acknowledged that the A4 device is no longer available, and we acknowledged the graphical data submitted in the revised agenda (see Section 6.0). BI committed to provide additional comparative in vitro data from the proposed and previous clinical studies, comparing the A5 low strength product to the A4 high strength product. BI committed to obtain data from 100 normally functioning drug product units of the A5 product used by patients in the proposed clinical study, and to compare these data with data from approximately 140 units of the A4 product from a previous clinical study.

- b. For your comparative high/low strength performance data on pages 27 and 28, indicate the number of cartridges and devices represented by each mean value.

BI’s Clarification Request of FDA’s Preliminary Response: The performance data on pages 27 and 28 represent the comparative data using Respimat A4 and A5 devices as well as the higher and lower concentration. For clarification, BI has updated the graphs with the requested information. (See Section 6.0 for graphs.)

Meeting Discussion: FDA acknowledged that the A4 device is no longer available, and we acknowledged the graphical data submitted in the revised agenda (see Section 6.0). BI committed to provide additional comparative in vitro data from the proposed and previous clinical studies, comparing the A5 low strength product to the A4 high strength product. BI committed to obtain data from 100 normally functioning drug product units of the A5 product used by patients in the proposed clinical study, and to compare these data with data from approximately 140 units of the A4 product from a previous clinical study.

- c. Provide additional assurances and data from an in-use testing situation, indicating that the characteristics and performance of the to-be-marketed formulation (low strength) product may be predicted from the higher strength in-use testing product data.

BI's Clarification Request of FDA's Preliminary Response: In lieu of an in-use study, BI proposes to demonstrate comparability by presenting performance data obtained from testing the clinical supplies used in the previous clinical study 1012.46 (140 units), and the supplies used in the ongoing clinical study 1012.56 (100 units as requested by FDA – see Question 4). Clinical study 1012.46 employed the higher strength solution with the Respimat® A4 device, while clinical study 1012.56 uses the lower strength solution with the A5 device. The data were/will be obtained from normally functioning supplies returned from the clinic, and therefore near the end of their in-use period. Does FDA agree?

Meeting Discussion: FDA indicated that BI's proposal as described in the briefing package and the clarification seemed reasonable in principle. It was understood that the drug product will be returned from the clinic after about three weeks of use (i.e., near the end of the use life) and it will be tested. The resulting data will be evaluated during NDA review, along with other data (e.g., data from the study discussed in Appendix 2 of the briefing package).

- 2.3** Briefing Package Question 3: The target delivered dose (and consequently the specification) for the commercial product is based on results of actuating the device in the sequential mode of actuation and all testing is performed in this mode. Does FDA agree with this approach?

FDA Preliminary Response: Yes, testing using the sequential mode of actuation appears to be appropriate and consistent based on the data you have provided in your briefing package. Describe your understanding of the observed increase in delivered volume over the life of the product. We cannot agree to a specific target or label claim at this time; these proposed acceptance criteria should be based on a significant dose content uniformity database.

BI Pre-Meeting Response: BI is satisfied with FDA's preliminary response and this question need not be discussed at the meeting.

- 2.4** Briefing Package Question 4: Does FDA agree that for clinical trial 1012.56, BI will investigate all apparently malfunctioning RespiMat® inhalers and test the functionality of the locking mechanism on 20 inhalers, since sufficient data on normally functioning devices have already been gathered from previous clinical studies?

FDA Preliminary Response: Because we are uncertain about the comparative performance of the A4 device with the high strength and A5 device with the low strength (see above in Section 2.2), provide full *in vitro* testing on 100 normally functioning drug product units returned from the clinical study. For drug product units that are reported by patients as malfunctioning, provide full *in vitro* testing and provide details including the reported malfunction(s) in each case.

BI's Clarification Request of FDA's Preliminary Response: BI will perform the same *in vitro* testing parameters on 100 normally functioning drug product units as what was done for clinical study 1012.46 (see Table 10 page 55 from briefing package of December 20, 2006).

Meeting Discussion: FDA stated that the proposal as described is reasonable. The resulting data will be evaluated during NDA review, along with other data (e.g., data from the study discussed in Appendix 2 of the briefing package).

- 2.5** Briefing Package Question 5: Does FDA agree to the proposed test parameters for control of the drug product and BI's approach on justification of Specifications for the proposed testing parameters?

FDA Preliminary Response: The proposed release specifications for the subject drug product are adequate from the standpoint of microbiological product quality. FDA is not commenting on the numerical values of the proposed acceptance criteria for other *in vitro* tests at this time. We have the following comments pertaining to the specification parameters:

- a. Add limits on individual cartridges to the proposed specifications for particulate matter, aerodynamic particle size distribution, assay, and volume of contents. Clarify whether the specifications for volume of contents and loss of mass are for individual cartridges.

BI's Clarification Request of FDA's Preliminary Response: BI appreciates FDA's advice and will take FDA's suggestions under consideration. However, there are some procedural limitations that prevent using single units and therefore require a pooling of the samples (b) (4)

Meeting Discussion: FDA recommended that BI provide scientific justification regarding the specifications in future submissions. FDA indicated that the proposed specifications should be based on data and the supporting data should be included in the NDA.

- b. For each specification, indicate the number of units tested on the specification sheet.

BI Pre-Meeting Response: BI is satisfied with FDA's preliminary response and this question need not be discussed at the meeting.

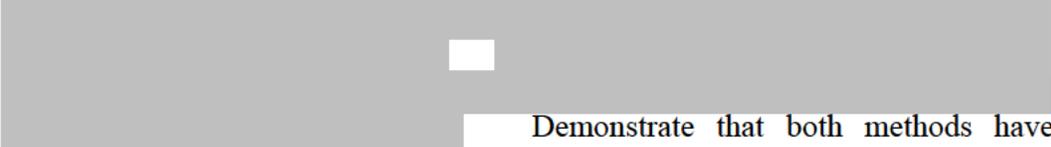
- c. The issue of inclusion or exclusion of "leachables" from drug product specifications will depend on our evaluation of the studies conducted (e.g., in the future NDA).

BI Pre-Meeting Response: BI is satisfied with FDA's preliminary response and this question need not be discussed at the meeting.

- d. The issue of "plume geometry" inclusion or exclusion from drug product specifications will be evaluated during NDA review of the adequacy of the spray pattern testing as a release test for the device (e.g., reproducibility, ability to distinguish acceptable from unacceptable performance).

BI Pre-Meeting Response: BI is satisfied with FDA's preliminary response and this question need not be discussed at the meeting.

- e. Spray content uniformity is normally based on drug content of the spray. (b)
(4)

 Demonstrate that both methods have comparable targets and precision over a large amount of data. This would be evaluated in your future NDA.

BI Pre-Meeting Response: BI is satisfied with FDA's preliminary response and this question need not be discussed at the meeting.

- f. The cascade impactor is normally used to determine the aerodynamic particle (droplet) size distribution (APSD) of the emitted aerosol. An alternative laser diffraction approach for measuring particle size distribution (PSD) would be precedent setting. The advantages of the cascade impactor include measurement of the APSD of the entire dose, and specific measurement of each active ingredient. As an alternative method, the laser diffraction method would have to be equivalent or better in controlling the APSD of the drug product. If homogeneity of the plume is claimed (e.g., in terms of droplet size distribution and drug content), it would have to be demonstrated with adequate data, taking into account, for example, the physical extent of the plume and the time period from initial emission of the plume to its ending.

BI Pre-Meeting Response: BI is satisfied with FDA's preliminary response and this question need not be discussed at the meeting.

2.6 Briefing Package Question 6: Does FDA agree with BI's proposed stability program as follows:

- a. The proposed testing parameters and testing points for the primary stability batches and

- b. The acceptability of the two in-use studies (intermittent use conditions and chemical stability after insertion of the cartridge) with the higher Combivent® Respimat® drug product concentration in support of the lower intended market concentration.

FDA Preliminary Response: The proposed testing parameters and testing points for the primary stability batches are adequate from the standpoint of microbiological product quality. Answers to your specific questions are as follows:

- a. Yes, based on information you have provided.
- b. Additional information is needed to assess this, including the information requested in our response to your Question 2 (above). Indicate how much data is represented by Table 8 (page 44) for each strength. In addition, the studies and data described in Appendix 2 will need to be evaluated.

BI's Clarification Request of FDA's Preliminary Response: As noted in question 2, we would like to get clarification on the term "microbiological product quality", whether this is a general or specific agreement to our proposal. If the term is specific, we seek clarification on the general terms of the proposal that may not be covered.

The data in table 8 are derived from a pooled solution of 20 cartridges from one batch per each strength.

Meeting Discussion: FDA indicated that BI's proposal as described in the briefing package and the clarification seemed reasonable in principle. FDA stated that "microbiological product quality" referred to general terms and did not intend to imply specific requirements. The resulting data will be evaluated during NDA review, along with other data (e.g., data from the study discussed in Appendix 2 of the briefing package).

- 2.7 Briefing Package Question 7: Does FDA agree to BI's proposal for the introduction of Physician samples and the studies proposed to demonstrate equivalent performance for a 60 actuation device?

FDA Preliminary Response: Your proposal as described in the meeting briefing package is satisfactory from a CMC perspective.

BI Pre-Meeting Response: BI is satisfied with FDA's preliminary response and this question need not be discussed at the meeting.

- 2.8 Briefing Package Question 8: Does FDA agree that this approach substantially minimizes the risk that patients may inadvertently mismatch the cartridge (b) (4)

FDA Preliminary Response: While your approach is reasonable (b) (4)

[Redacted]

BI's Clarification Request of FDA's Preliminary Response: BI would like to clarify that (b) (4)

[Redacted]

[Redacted]

We appreciate the opportunity to further discuss this issue with FDA.

Meeting Discussion: FDA reiterated that BI's approach is reasonable (b) (4)

[Redacted]

3.0 ISSUES REQUIRING FURTHER DISCUSSION

We have the following additional comments:

- 3.1 You are reminded of comments documented in our meeting minutes of the previous End of Phase II meeting, which took place on January 17, 2003, for this IND. (b) (4)

[Redacted]

BI Pre-Meeting Response: BI is satisfied with FDA's preliminary response and this question need not be discussed at the meeting.

3.2 Regarding your statement on page 23 of the 12/20/2006 meeting package:

"Release testing of the assembled Respimat inhaler is conducted with cartridges containing either a placebo solution, or one of the inhalation solutions developed for use with the device."

Since we view the drug product as including both the device and the specific drug formulation, testing should be performed to release a specific batch of devices with a specific batch of cartridges. This includes testing with the cartridges containing the specific drug formulation, for Combivent in this case. This concern was stated in our IND 57,948 meeting minutes for the meeting on January 17, 2003 (response to item #8)

(b) (4)

BI's Clarification Request of FDA's Preliminary Response: BI wishes to clarify the statement on page 23 of the 12/20/2006 briefing package pertaining to the release testing of the Respimat® device by the device manufacturer (BI microParts). The Respimat® device is considered a container/closure component of the drug product, and the release of the device by the device manufacturer employs testing with cartridges containing either placebo solution, or an authentic solution of a drug substance.

For release of the drug product, BI is following the Agency's advice as described above,

(b) (4)

all performance parameters are tested on that specific combination.

Meeting Discussion: FDA acknowledged BI's clarification. The participants discussed the definition of a batch of drug product.

(b) (4)

BI committed that each drug product batch will be fully tested with drug product specifications.

(b) (4)

3.3 Provide to your future NDA, in-use data to demonstrate whether foreign particulates increase over drug product life.

BI's Clarification Request of FDA's Preliminary Response: BI would like to clarify what FDA means by in-use data in this context.

Meeting Discussion: FDA clarified that the in-use data comment pertained to the in-use situation after the patient connects the cartridge to the device, and during the period over which the drug product is used, before it locks out further use.

BI clarified that the device uniblock component, which contains the nozzles, also functions as a final filter for the dose (b) (4) therefore it assures that any particulates from the device are not emitted with the dose. FDA asked BI to provide some one-time characterization data to show that particulates are not emitted by the drug product through life of device and cartridge. BI indicated that any available data would be included in future submissions, and would be used to support the scientific justification of foreign particulate control. FDA asked if there was any observed problem with the filter clogging due to particulates in the device, and BI responded that there have been no observed problems.

- 3.4** Provide information in the NDA pertaining to the purity profile of edetate disodium and benzalkonium chloride (page 13).

BI Pre-Meeting Response: BI will take this under advisement in preparation of the Combivent® Respimat® NDA. This topic need not be discussed at the meeting.

- 3.5** For each of your stability studies, provide summary data in your future NDA in tabular and graphical formats, organized by individual parameters and separated by storage condition and batch number. Graphical presentations should include proposed limits, and individual as well as mean data.

BI Pre-Meeting Response: BI is satisfied with FDA's suggestion for tabular and graphical formats, so this topic need not be discussed at the meeting.

- 3.6** Following are preliminary comments/discussion on the device DMF (DMF (b) (4) as requested.

3.6.1 The following comments are based on a cursory look of the DMF and are not comprehensive. We cannot provide a complete review until this DMF is referenced in an NDA:

3.6.2 Include APSD by CI and DCU in the device specifications.

BI's Clarification Request of FDA's Preliminary Response: As stated in the response to section 3.2, release testing of the Respimat® device is the first step in the chain of testing performed. Particle Size Distribution by laser diffraction and Delivered Mass are performed as part of the release testing requirements.

(b) (4) in the production of the drug product at BI, all performance parameters are tested on that specific combination which includes APSD by CI and DCU as release requirements of the drug product.

Meeting Discussion: FDA indicated that the proposed device performance testing differs from the performance testing to be performed with the drug product. Specifically, the data obtained from the use of a laser diffraction method provides data that is not directly comparable to that from the cascade impactor method. Testing the device as proposed may be acceptable, as long as the test parameters are fixed and effectively assure that the drug product, when tested, will pass its performance specifications. BI acknowledged FDA's comments.

3.6.3 Provide information about the composition of each device component.

BI's Clarification Request of FDA's Preliminary Response: BI requests further clarification on the need to provide the composition for each device component. It is BI's understanding that all critical components of the device will be appropriately described and/or reference provided to the supplier's DMF.

Meeting Discussion: FDA expressed concerns that if composition of components change, unbeknownst to BI, that the performance of the part may be impaired. If the composition is not known, then any composition is possible. FDA recommended that BI obtain and maintain as much knowledge as possible about the composition of each component.

FDA acknowledged that there are proprietary concerns that may limit information about composition that the manufacturer of the material or component will provide. BI acknowledged that "critical components" which are defined as contacting the patient's mouth and/or the drug formulation, have supporting information in DMFs. FDA said that there were other components which may not function properly if the composition changed. (b) (4)

(b) (4) FDA said that this could be part of BI's justification. Nevertheless, FDA encouraged BI to learn more about the composition of the other components (b) (4) FDA suggested that a one time extraction study for the "non-critical" components could provide some information about the composition which could confirm BI identity testing.

3.6.4 Perform identity tests on "secondary" device components.

BI Pre-Meeting Response: BI appreciates FDA guidance on this topic and we will take it under advisement for the preparation of the Combivent® Respimat® NDA.

3.6.5 Perform USP <87>/<88> testing for critical device components.

BI Pre-Meeting Response: BI appreciates FDA guidance on this topic and we will take it under advisement for the preparation of the Combivent® Respimat® NDA.

3.6.6 Discuss your analytical sampling plans.

BI's Clarification Request of FDA's Preliminary Response: BI requests further clarification on this comment.

Meeting Discussion: No further discussion of this discussion point occurred at the meeting.

3.6.7 It is our understanding that all extractable data, methods, validations, etc. will be included in the relevant NDAs.

BI Pre-Meeting Response: Yes.

3.6.8 Indicate whether you have performed risk analysis during development of the device/drug product (e.g., failure modes and effects analysis).

BI Pre-Meeting Response: Yes, BI has performed risk analyses during development of the device/drug product.

4.0 ACTION ITEMS

No specific action items resulted from the meeting.

5.0 CONCURRENCE:

{See appended electronic signature page}

Scott N. Goldie, Ph.D.
Regulatory Health Project Manager for Quality
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment

{See appended electronic signature page}

Blair Fraser, Ph.D.
Division Director
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment

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

/s/

Scott Goldie
2/23/2007 04:13:54 PM

Blair Fraser
2/23/2007 06:28:32 PM



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

FACSIMILE TRANSMITTAL SHEET

DATE: May 15, 2006

To: BIPI	From: LCDR Lori Garcia Regulatory Project Manager
Company: Jeff Snyder	Division of Pulmonary and Allergy Products
Fax number: (203) 837-4928	Fax number: 301-796-9718
Phone number: (203) 778 7727	Phone number: 301-796-1212
Subject: I57,948/04-26-2006 Meeting minutes	

Total no. of pages including cover: 9

Comments:

Document to be mailed: YES xNO

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MEMORANDUM OF MEETING MINUTES

MEETING DATE: April 26, 2006
TIME: 10:30am-12:00pm EST
APPLICATION: IND 57,948
DRUG NAME: Combivent Respimat
TYPE OF MEETING: Type B/EOP II
MEETING RECORDER: Lori Garcia, R.Ph.
MEETING CHAIR: Badrul Chowdhury, M.D. Ph.D.

FDA ATTENDEES:

Division of Pulmonary and Allergy Drug Products

Badrul Chowdhury, M.D., Ph.D., Division Director
Eugene Sullivan, M.D., Deputy Director
Anthony Durmowicz, M.D., Clinical Reviewer
Lori Garcia, RPh., Regulatory Project Manager
Feng Zhou, M.S., Statistical Reviewer
Ruthanna Davi, M.S., Statistical Team Leader
Sayed Al-Habet, Ph.D., ClinPharm Reviewer
Emmanuel Fadiran, Ph.D., ClinPharm Team Leader

EXTERNAL CONSTITUENT ATTENDEES:

Boehringer Ingelheim Pharmaceuticals, Inc.

Marty Kaplan, M.D., J.D., VP, Drug Regulatory Affairs
Bernd Disse, M.D., Therapeutic Area Head-Pulmonary
Sabine Kattenbeck, Ph.D., International Project Manager
Christoph Hallman, M.D., International Project Manager
Mo Ghafouri, Ph.D., Sr. Assoc. Dir., Clinical Operations
Eben Rubin, M.D., Director, Clinical Operations
Helen Dewberry, BSc., Project Statistician
Shalendra Menjoge, Ph.D., Director, Respiratory Statistical Projects
Jeff Snyder, Director, Drug Regulatory Affairs
Damon Daulerio, MBA, Manager, Drug Regulatory Affairs

BACKGROUND:

BIPI submitted a meeting request dated February 14, 2006, for a Type B End of Phase II meeting to discuss the proposed Phase III protocol supporting registration of Combivent Respimat. A briefing package for this meeting was submitted on March 28, 2006. Upon review of the briefing package, the Division responded to BIPI's questions via fax on April 24, 2006. The content of that fax is printed below. Any discussion that took place at the meeting is captured directly under the relevant original response including any

changes in our original position. BIPI's questions are in ***bold italics***; FDA's response is in *italics*; discussion is in normal font.

MEETING OBJECTIVES:

To further clarify and discuss the responses faxed to BIPI on April 24, 2006.

DISCUSSION:

Clinical

- 1. Does the Agency agree with the proposed treatment groups, doses/regimen, analysis plan, duration of treatment, and sample size of the pivotal Phase 3 trial?***

FDA response:

The proposed treatment groups, doses/regimen, and duration of treatment are acceptable. However, your proposal [REDACTED] (b) (4), without formal hypothesis testing is not acceptable. The study should establish non-inferiority for these comparisons (see minutes of the 12/21/05 meeting). In order to achieve this, the sample size may need to be adjusted. The non-inferiority analysis, including appropriate justification of the non-inferiority margin, should be consistent with the ICH E10 guidance.

Discussion:

BI requested further discussion of the issue of comparability vs. non-inferiority. BI made reference to the 1994 Division of Pulmonary and Allergy Drug Products Points to Consider document for "switch" products entitled, "Clinical development programs for MDI and DPI drug products," stating that this comparability standard has been used in several other development programs in the past. BI proposed that [REDACTED] (b) (4). BI asked if they would be held to a strict interpretation of non-inferiority, or if the Division would allow some flexibility. The Division stated that the 1994 "Points to Consider" document is an old document and is not a Guidance Document, and was intended to address the change from a single ingredient product to another single ingredient product. The principles change for a combination product and the document can not be applied in this case. The Division noted that it had been specified at the 12/21/05 meeting that non-inferiority must be shown.

The Division elaborated on the rationale for requiring that non-inferiority be shown for this combination product, stating that BI needs to demonstrate non-inferiority because of the results from prior studies which showed that 1 component of the combination product was better than the combination product at the end of the dosing interval. The Division is willing to look at the first part of the dosing interval alone to establish the effect of the albuterol, but it also needs to be established that at the end of the interval that no loss of efficacy has been caused by the combination product. The Division acknowledged that demonstration of non-inferiority is a high bar, but noted that it is necessary based on the concerning results from the prior studies.

The Division questioned why BI proposed (b) (4)
The Division referred to page 39 of BI's briefing package (submitted March 28, 2006) which states,

(b) (4)

(b) (4)

In regards to the history of the development plan for Combivent Respimat, the Division referred to page 36 of BI's briefing package (submitted March 28, 2006), which states,

“(b) (4)
”

The Division stated that the above statement is not accurate and that its conclusions regarding the (b) (4) were based on “change from test day baseline” analyses, as agreed upon at the February, 1991, EOP2 meeting for that product. (b) (4)

The Division stated that it does not understand the rationale behind BI's hypothesis. Specifically, in Study 1012.46 (b) (4) the combination of albuterol and ipratropium bromide did not perform as well as the single agent (ipratropium bromide) late in the dosing interval. The rationale

behind BI's hypothesis that a lower dose combination will behave differently is not clear. The Division suggested that it may be wise to gather additional Phase 2 data to explore the issue before proceeding to Phase 3. In addition, if BI's hypothesis that the lower dose combination will be superior to both single agents is true, establishing non-inferiority should not be difficult. In fact, if the "problem" will be solved by using a lower dose, BI could potentially propose a superiority study based on the entire dosing interval, comparing the combination product to each of its components. The Division advised BI to seek further advice if it intends to alter the approach.

The Division noted that the BI's main objection to the non-inferiority approach seems to be that this analysis incorporates the variability in the data but stated that this is precisely what is necessary. An analogous proposal in a superiority setting would be simply to compare 2 point estimates, if the point estimate for one product is better than that of the other then that product is concluded to be better with no incorporation of the variability or sample size into the assessment. Clearly, this is not acceptable in the superiority setting, and similarly, it is not acceptable in a non-inferiority analysis. (b) (4)

- 2. In Phase 3 study 1012.46, ECGs were obtained in 1118 COPD patients. ECGs were performed pre- and post-treatment at screening and on test days 1, 29, and 85. ECG's were reviewed and analyzed centrally by (b) (4) and it was concluded that there was no evidence of any clinically relevant changes in ECGs. Based on the extensive ECG evaluation with a higher dose of COMBIVENT RESPIMAT (40mcg/200mcg) than the doses proposed for the current 1012.56, does the Agency agree that no additional ECG monitoring/data is necessary in the 1012.56 study?***

FDA response:

You may choose to use data from 1012.46 to support the cardiac safety of the proposed product; however, Study 1012.56 should include some ECG monitoring. Note that the Division has not yet reviewed the ECG findings from study 1012.46. Findings from that study may be described in the product label.

Discussion:

BI proposed to do entrance and exit ECGs in Study 1012.56. The Division noted that it did not have a specific number of ECGs in mind, but recommended that BI add more. The Division reiterated that it had not seen the ECG data from Study 1012.46 and stated that BI would be at more of a risk not to have ECG data available for the proposed dose.

- 3. Pharmacokinetics (PK) studies were conducted in 109 COPD patients in the 1012.46 study. Based on the extensive PK information that is already available,***

a limited PK sampling from approximately 150 patients will be used to establish the pharmacokinetics of the lower dosages proposed in study 1012.56. Does the Agency agree that the proposed pharmacokinetic characterization is sufficient to support the PK profile (in the NDA)?

FDA response:

The approach appears to be reasonable based on your summary and conclusions submitted in the briefing package. The data will be reviewed at the time of NDA submission.

Regulatory

- 1. The Agency had suggested in a previous discussion that an ipratropium Respimat arm would be the most appropriate monoproduct comparator to include in the proposed study. Is the rationale for the choice of comparator (Ipratropium bromide (RESPIMAT) Inhalation Spray) acceptable?***

FDA response:

The choice of IB-R as the comparator is appropriate, and will allow for a comparison of the pharmacologic effect of the combination product and one of its components (IB), without confounding effects that might be introduced by the use of a different formulation (e.g. MDI). Such a comparison is consistent with the combination policy. However, as discussed at the 12/21/05 meeting, the NDA submission must include sufficient “bridging” data to establish the pharmacodynamic effect of IB-R.

Discussion:

BI stated that they believe sufficient data are available to support a clinical bridge between the IpBr Respimat and Atrovent HFA for the Combivent Respimat NDA. BI proposed to not do any additional clinical trials to establish a formal comparison between Atrovent HFA and IpBr Respimat, and asked if their interpretation of the FDA response seems reasonable. The Division explained the rationale for requiring bridging data. As currently designed, the study may be able to establish the benefit of the combination product over ipratropium alone, but there must also be data in the application to establish that ipratropium alone is, in fact, effective.

- 2. During previous discussions with the Agency, it was agreed that no additional toxicology studies are needed to support the COMBIVENT RESPIMAT NDA if no concerns arise from the evaluation of the safety of the degradants, extractables, leachables, and impurities in the product. With respect to this and given our plan to cross-reference to the COMBIVENT CFC MDI NDA 20-291 for toxicology, pharmacology, and pre-clinical ADME information, does the***

Agency agree that adequate preclinical information is available and that no additional preclinical information will be needed to support a COMBIVENT RESPIMAT NDA submission?

FDA response:

No additional nonclinical information is needed for any ingredients of the product. The NDA submission needs to address and evaluate the safety of impurities as per ICH Guidances Q3A and B, as well as leachables and extractables that are present in the drug substance and/or product. Additional nonclinical data will be needed if any of these substances raise a safety concern.

- 3. *Does the Agency agree that the proposed clinical trial in conjunction with completed clinical studies evaluating the safety/effectiveness of COMBIVENT RESPIMAT in patients with COPD will provide a sufficient basis for the submission of an NDA?***

FDA response:

As discussed at the 12/21/05 meeting, the Division does have reservations regarding the plan to perform a single “pivotal” clinical trial with a new, lower dose product. This is particularly the case since previous studies of this product [REDACTED] (b) (4) have failed to demonstrate that the combination is superior to each of its components. However, as discussed at the 12/21/05 meeting, if the efficacy findings are robust and convincing, a single trial may be sufficient to establish efficacy.

In terms of safety, the extent of exposure appears adequate for NDA filing. Interpretation of the safety findings will be undertaken during review of the NDA.

Device durability/reliability should be examined in Study 1012.56. This should include directed questionnaires to detect device malfunction, as well as collection and in vitro testing/analysis of any devices reported to have malfunctioned during the study. A sample of devices that have apparently functioned normally during the clinical trial should also be collected and tested near the end of the life of the device.

Discussion:

Regarding device reliability, the Division suggested that BI design a questionnaire that asks at least 3-4 questions about the device, along the lines of the following; “Have you had any problems with the device?” “Did the drug come out of the device?” and “Did the device function properly and re-cock after the dose?” The Division recommended that BI capture as many variables as possible about the device.

The Division reminded BI that the Phase III study should include appropriate patient instructions for use of the device, which would then appear in the product label. If a device issue is identified in the Phase 3 study it will be very difficult to establish that it can be adequately addressed with new patient instructions without repeating the study.

Lori Garcia, R.Ph., Regulatory Project Manager

Drafted: LGarcia/April 28, 2006

Initialed:

RDavi/May 2, 2006

ADurmowicz/May 9, 2006

ESullivan/May 9, 2006

BChowdhury/May 10, 2006

Finalized: LGarcia/May 11, 2006

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

/s/

Lori Garcia
5/11/2006 09:01:48 AM

Memorandum of Telephone Facsimile Correspondence

Date: October 24, 2003

To: Theresa Maloney, R.Ph.
Sr. Associate Director, Drug Regulatory Affairs

Fax: 203-791-6262

From: Christine Yu, R.Ph.
Sr. Regulatory Management Officer

Subject: IND 57,948 Combivent Respimat Inhalation Spray
Minutes of September 24, 2003 pre-NDA meeting

Reference is made to the meeting/teleconference held between representatives of your company and this Division on September 24, 2003. Attached is a copy of our final minutes for that meeting/teleconference. These minutes will serve as the official record of the meeting/teleconference. If you have any questions or comments regarding the minutes, please call me at (301) 827-1051.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you received this document in error, please immediately notify us by telephone at (301) 827-1050 and return it to us at FDA, 5600 Fishers Lane, HFD-570, DPDP, Rockville, MD 20857.

Thank you.

BIPI submitted a request for a pre-NDA meeting on June 13, 2003, to discuss their plans for submitting the NDA for Combivent Respimat in September 2004. Combivent Respimat is being developed by BIPI as a CFC replacement for Combivent Inhalation Aerosol. Briefing packages for the meeting were received August 21, 2003.

Agenda (order based on the questions included in the briefing package)

Clinical & Clinical Pharmacology & Biopharmaceutics (CPB)
Chemistry, Manufacturing & Controls (CMC)
Preclinical
Common Technical Document (CTD) and electronic submissions

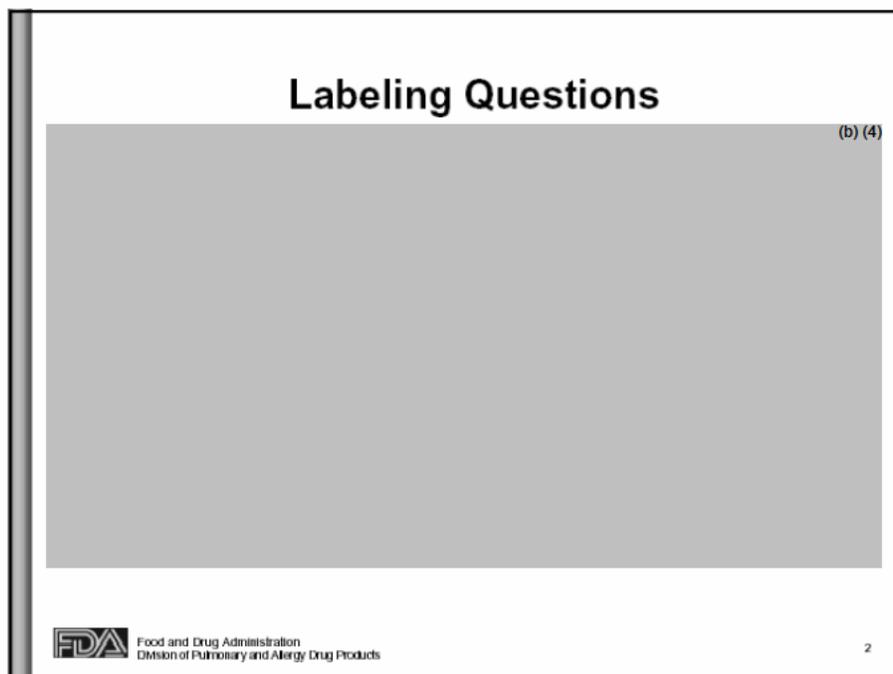
Guidances for Industry referenced during the meeting

Guidances represent the Food and Drug Administration's (FDA's) current thinking on a topic. They do not create or confer any rights for or on any person and do not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

MINUTES

The slides presented by the Division include BIPI's questions, followed by the Division's responses. Additional discussions during the meeting are captured between the slides.

Clinical/Clinical Pharmacology & Biopharmaceutics (CPB)



Labeling Questions



Labeling Questions

1.3 Does the Division have any general comments on the draft labeling components included in the pre-NDA meeting package?

There are no other comments prior to the review.

Clinical Questions

2.1 Based on the draft Table of Contents provided for Module 5, does the Division agree with the general organization of the clinical data for the NDA?

This is acceptable from the clinical point of view. However, more comments will be made at the end of the discussion relating to the electronic format of the submission.

Clinical Pharmacology Questions

Question 2.2:

➤  (b) (4)
The Human Pharmacokinetics Summary (2.7.2) will primarily focus on the pharmacokinetic data for COMBIVENT RESPIMAT from the Phase III study 1012.46. As the pharmacokinetic data from the monocomponent RESPIMAT studies are marginally pertinent to the COMBIVENT RESPIMAT drug product, this document will present them as secondary supporting studies. Does the Division agree with this approach?

Answer:

➤ *Yes. However, since data from clinical trials conducted with the monocomponents will support the safety of COMBIVENT RESPIMAT, the division will expect PK data comparison between the monocomponents and its respective active comparators.*

BIPI asked for clarification on the Division's response above, adding that PK data would be provided for the COMBIVENT RESPIMAT.

The Division replied that since safety data from the monocomponents could be used to support the COMBIVENT RESPIMAT program, then a comparison of the systemic exposure of the components

from COMBIVENT RESPIMAT with the monocomponents would provide an additional link to the safety data.

Clinical Pharmacology Questions, cont.

Question 2.3:

- At the COMBIVENT RESPIMAT Clinical End-of-Phase II Meeting, the Division reminded BIPI that submission of comparative Biopharm studies is a requirement for a 505(b)(2) Application (Reference FDA's 28 May02 Meeting Minutes). (b) (4)
(b) (4) BIPI requested, (b) (4) a waiver for in-vivo bioequivalence and bioavailability studies as specified under 21 CFR 320 while providing in-use pharmacokinetic data in patients. Does the Division agree that a request for a waiver is an appropriate strategy for the COMBIVENT RESPIMAT NDA?

Answer:

- Yes. However, the agency recommends that in the proposed Phase III clinical trial 1012.46, you assess the PK of the components not only at steady state, but also following single administration.

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BIPI added that since the clinical trial had already started, they would not be able to provide PK data following single administration. The Division indicated that this would be acceptable.

ADDITIONAL COMMENTS

- We recommend that you assess the effect of age and gender on the pharmacokinetics of ipratropium bromide/albuterol sulfate delivered from the COMBIVENT RESPIMAT.

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Clinical Questions

2.4 Considering that there is only one COMBIVENT RESPIMAT Phase III Trial (1012.46) and that mono-component RESPIMAT data are only relevant for dose selection and long term excipient and RESPIMAT inhaler safety, does the Division agree with the proposed organization of the Clinical Summary of Efficacy (2.7.3)?

- **Efficacy will be based on the results of the 12-week pivotal trial (1012.46). Approval will depend upon the demonstration that Combivent Respimat is superior to Ipratropium Respimat as well as placebo.**

Clinical Questions

- 2.5 Due to inadequate sample size, no formal tests of hypotheses will be conducted to assess the comparability of COMBIVENT RESPIMAT and COMBIVENT CFC across subgroups such as age, race, gender, severity of disease. The sample sizes, means and standard errors will be provided for each sub-group and treatment groups (i.e., COMBIVENT RESPIMAT, COMBIVENT CFC and placebo). Does the Division consider this appropriate?

- **This is acceptable as long as the descriptive statistics are provided**

Clinical Questions

- 2.6 The safety data for the Clinical Safety Summary (2.7.4) will be organized into 3 major sections (1) 1012.46 data with a comparison of COMBIVENT RESPIMAT to COMBIVENT Inhalation Aerosol to Placebo, (2) 244.2484 data which will provide the long term (6 month) safety of the excipients and the RESPIMAT device and (3) other miscellaneous safety data. Additionally, the subgroup analyses of the Phase III Trial 1012.46 will be provided in the clinical trial report. Does the Division agree this is a reasonable approach for meeting the requirements for an integrated safety analysis as described un 21 CFR 314.50(5)(vi)(a)

- **This is acceptable**

Clinical Questions

- 2.7 The Division has been interested in paradoxical bronchospasm. This will be discussed in the Clinical Safety Summary (2.7.4). The long-term (six-month) data on the excipients and RESPIMAT device from the 244.2484 Trial will be presented and discussed in Section 2.7.4.2. Additionally, the results from the COMBIVENT RESPIMAT Phase III Trial (1012.46) will be provided and discussed in Section 2.7.4.2.1. Does the Division agree with this approach?

- **This is acceptable. We would also like to see a direct comparison between the Respimat and CFC control groups from the pivotal trial (1012.46) as this will be a test of the effects of the excipients.**

Questions

- 2.8 For the Safety Summary Post-Marketing Data Section (2.7.4.4), BIPI plans to have a brief narrative describing where COMBIVENT Inhalation Aerosol has been marketed, how long the product has been marketed, the number of patients exposed and statements related to whether or not the drug has been withdrawn anywhere. This is based on the assumption that the profiles of the COMBIVENT RESPIMAT and COMBIVENT Inhalation Aerosol are shown to be similar in the Phase III Trial 1012.46 and that the COMBIVENT RESPIMAT package insert will essentially utilize sections from COMBIVENT Inhalation Aerosol approved labeling. Does the Division agree with this approach?
- **In addition to the above, we need an integrated summary of the post-marketing adverse event reports that have been submitted since the last annual report for Combivent CFC**

Clinical Questions

- 2.9 Based on the assumption of no significant findings in the COMBIVENT RESPIMAT Phase III Trial 1012.46 and the fact that COMBIVENT Inhalation Aerosol has a long term established safety profile, BIPI is not planning to have a Management Risk Assessment Plan as part of the NDA. Does the Division agree with this approach?
- **This is acceptable**

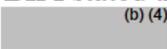
Additional Comments

(b) (4)



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BIPI stated that they will not be conducting a separate trial for patient handling of the device in adults  (b) (4) but will be capturing the data in the pivotal trial.

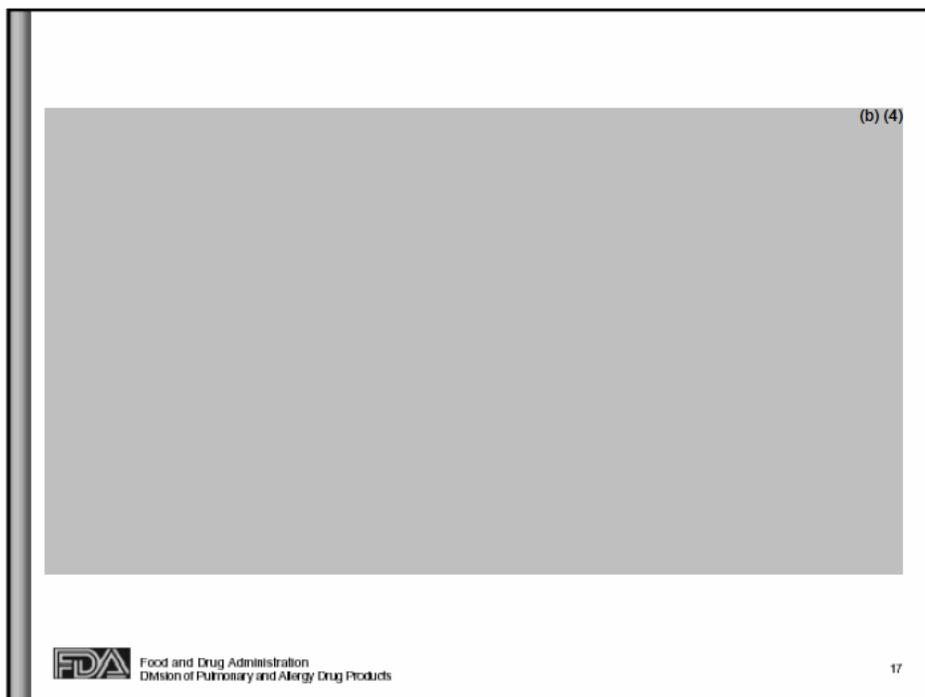
Additional Comments

- **As discussed at the EOP2 meeting in May 2002, device failure should be an outcome measure in all of the treatment arms.**
- **You are submitting SAS data sets for only the pivotal trial (1012.46). We need any data sets that exist for the other trials as well.**
- **We would like to see the Laboratory values reported in a shift table.**

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In response to comment in the second bullet above, BIPI stated that they will provide data available to the best of their abilities.



The Division stated that determination of efficacy is a review issue. [REDACTED] (b) (4)

[REDACTED] Combivent Respimat would have to show that it is as efficacious as the Combivent inhalation aerosol and the ipratropium Respimat.

BIPI noted that although the albuterol/ipratropium products are used QID or every 4-6 hours, [REDACTED] (b) (4)

The Division stated that the combination policy is not being applied to this drug product, and no additive effects are expected. Whether efficacy is supported for [REDACTED] (b) (4) hours would be a review issue.

BIPI asked if the Division would review the data before NDA submission.

The Division stated that they could not guarantee a review would be performed before a NDA is submitted. [REDACTED] (b) (4)

[REDACTED] (b) (4)

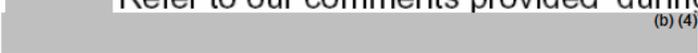
Chemistry, Manufacturing, and Controls (CMC)

General Comments

- >  (b) (4)
- > **Cross – references (pages if possible) for ease of the review**
 - ◆ To other CMC parts/data in submission
 - ◆ To other disciplines data and information
- > **We can not provide comments on submitted specifications or data in the meeting package before the review.**

3. CMC Related Questions

3.1 Does the FDA agree with our proposal on the level of information to be presented in the NDA for both drug substances *versus* the information incorporated from the DMFs? (155-165)

- > Yes. Drug substance acceptance specifications submitted to the NDA should be identical to or better than the current specifications in DMFs  (b) (4) and  (b) (4) Refer to our comments provided during  (b) (4)  (b) (4) and address any outstanding issues.

The Division added that BIPI should indicate who performs which test, and with what frequency. Re-test/expiry date and testing protocol should be clearly outlined.

3. CMC Related Questions

3.2 Does the FDA agree on the structure and layout of the presented Pharmaceutical Development Report, in particular the location of the information on the Respimat device development? (170-178)

- Yes. Provide cross-references in tabular form linking changes in formulation and device to the pre-clinical, clinical, and stability studies. Include batch numbers and references to the data evaluating the impact of changes on the drug product performance.

3. CMC Related Questions

3.3 FDA's current thinking on a pre-approval inspection for the manufacture of the Respimat device and if such an inspection were to be carried out, under what GMP 21 CFR regulation would it be performed? (180)

- We treat the Respimat device as an integral part of the drug product and will primarily rely on the adequate release specifications and provided data, including the in-use studies. Final decision about inspection of the device facility will be made at the time of submission by CDER in consultation between the Office of Compliance and DPADP.

The Division noted that if an inspection is needed, Office of Compliance can involve CDRH inspectors. When the NDA is submitted, the Agency will evaluate it to see if there is a need for CDRH inspectors to accompany CDER inspectors. The Agency emphasized the importance of adequate CMC data from in-use studies. BIPI should prepare the inspection documents following procedures for CDER. The Agency is not necessarily concerned that a specific format is followed as long as the technical approach is satisfied for both CDER and CDRH.

3. CMC Related Questions

3.4 Does the FDA agree with our proposal to submit a detailed description of the manufacturing process in lieu of an actual Master Batch Record? (182-186)

- Our preference is that in addition to the description of the manufacturing process you provide a certified translation of the Master Batch Record.

BIPI stated that their description of the process would provide better detail. The Master Batch Record would be informational only.

The Division noted that in past experience, sometimes significant changes were subsequently made when a drug company only submitted a general description of the manufacturing process, without specific numbers, to the NDA.

3. CMC Related Questions

3.5 Does the FDA agree with the proposal for batch definition(s) and the release concept for the Combivent Respimat Inhalation Spray drug product? (191)

➤  (b) (4)

➤

➤

➤

➤

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BIPI responded that they would provide more explanations with the NDA submission.

3. CMC Related Questions

3.6 Does the FDA agree with the proposed program for extractables characterization and control of the components of the Repimat device and cartridge as proposed in the June 17, 2003 submission? (199)

➤ Yes, with the understanding that the details of the proposal were not provided and reviewed.

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3. CMC Related Questions

3.7 Does the FDA agree with our proposal on the location of information for the Respimat device? (199)

- Our preference is to have all information and data pertaining to the to-be-marketed drug product in the NDA section for Container Closure System (3.2.P.7). This includes characterization data and the results of control extraction studies. Changes in the device and formulation during development should be described in the Pharmaceutical Development section (3.2.P.2) and appropriate information pertaining to the to-be-marketed product may be summarized or repeated here for comparison purposes, with appropriate references to other sections.
- Provide a summary table of DMFs, holders and references to LOAs.
- Include the specifications and clearly identify party responsible for release and acceptance testing, including components.

3. CMC Related Questions

3.9 Does the FDA agree with the proposal to submit 2 executed batch records, one from each of the 2 sets of primary stability batches as described in Section 3.2.R.1? (208)

- Yes. Provide information on how representative are these batches in terms of size and manufacturing process, in comparison to the clinical and to-be-marketed batches of the drug product.

3. CMC Related Questions

3.10 Does the FDA agree on our proposal to submit with the Regional Information a Methods Validation package only for the drug product analytical methods? (208)

- Yes, provided that the validated methods for drug substance are submitted to the updated DMFs and those will have adequate status upon review.

(b) (4)

As an over view of the CMC section, the Division commented that although many reports may be provided, a lack of cohesiveness to the submission (i.e., lacking narrative linking all data and information into a unified whole), will delay effective CMC review. Characterization studies should be performed with the to-be-marketed device and formulation.

Pharmacology & Toxicology

Question 4.1 (nonclinical)

Based on the draft Table of Contents provided for Module 4, does the Division agree with the general organization of the nonclinical data for the NDA?

Response:

Suggest placing all studies supporting the impurity qualifications under the item 4.2.3.7.6 (CTD) that is reserved for impurities.



Question 4.2 (nonclinical)

Does the Division agree with the proposed organization and presentation of data for the Module 2 – Nonclinical Summaries and Tabulates?

Response:

**Summaries (2.6) appear acceptable;
Provide the nonclinical overview section (Item 2.4).**



Additional Nonclinical Comments

- **Suggest providing information that bridges the current application with the previous applications.**
- **Suggest updating the nonclinical data in CTD format.**
- **Need to evaluate the safety of impurities, degradants, extractables and leachables.**



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Combivent Respimat, IND 57,948
Nonclinical, Pre-NDA mtg, Sept. 24., 2003

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BIPI asked the Division to clarify its suggestion of “providing nonclinical information that bridges the current application with previous applications.” BIPI stated that it was burdensome and demanded extra resources.

The Division responded that the suggestion was not a requirement, although such information would be helpful in facilitating the review process.

Electronic Submissions

General Considerations / Observations

- Try to minimize the paper “review” portion of the submission
 - ◆ If primarily an “electronic” submission, only the technical sections should have paper copies (along with Module 1 which is regional and consists mainly of those forms requiring signatures).
 - ◆ See the “Guidance for Industry; Providing Regulatory Submissions in Electronic Format – NDAs”, IT3 dated January 1999 for details

General Considerations / Observations

(Continued)

We have published two new “Guidance for Industry” documents concerning the eCTD:

- ◆ Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions, 8/2003
- ◆ M2 eCTD: Electronic Common Technical Document Specification

These might give you some additional guidance and an insight into where the FDA is heading with both the electronic and paper submissions.

#2 - Clinical Related Questions

General 2.1: Based on the draft Table of Contents provided for Module 5, does the Division agree with the general organization of the clinical data for the NDA?

- The TOC is acceptable, *however*, take care in creating “extra” sub-categories.
- Granularity and Nomenclature should adhere as strictly as possible to Guidance(s)
- Where multiple “documents” fall under a given category, they can “run on” to each other under that heading with no additional numbering created.
- In the paper versions, these can be further “Tabbed” to separate, without creating additional “granularity.”

#2 - Clinical Related Questions

Safety 2.6: The safety data for the Clinical Safety Summary (2.7.4) will be organized into 3 major sections... Does the Division agree this is a reasonable approach for meeting the requirements for an integrated safety analysis as described under 21 CFR 314.50(5)(vi)(a)?

- While the content may fulfill the cited requirement, it does not meet the FDA / ICH requirement for structure and organization of the data.
- The CTD instrument is fairly rigid in its construct and cannot be “manipulated” nor “massaged” to fit a presentation effect. Refer to “Guidance for Industry, M4E: The CTD – Efficacy”, issued August 2001.
- There are several Q & A documents posted in the Guidances section(s) that can help you deal with the construct and placement of data in a CTD “document”.
- Future “automated” review tools are based on the established structure and format as described by the ICH

#5 Electronic Submission Related Questions

5.1 Does the Division agree with the proposal that datasets (xpt files) will only be provided for the Phase III Combivent Respimat study?

- Perceived relevancy of data is not the determining factor for inclusion of data sets.
- If only Trial 1012.46 has datasets, other studies being in an older legacy format, then the proposal is acceptable from a technical standpoint.
- Other datasets, if available, and at the Review Division's discretion, may be requested for inclusion as SAS transport files (xpt).



#5 Electronic Submission Related Questions

5.2 The case report form (crf) folder will be organized by trial, investigator, patient ID. The bookmarks and crf table of contents will include the investigator site. Does the Division agree with this approach?

- Acceptable from a technical standpoint with adequate bookmarks.



#5 Electronic Submission Related Questions

5.3 ECGs for the Phase III Trial 1012.46 are being recorded digitally. ...
Does the Division agree that it is acceptable to have the ECG digital data available only upon request?

- Yes
- There is ongoing discussion within the FDA on how best to handle the “odd” types of data.
- Currently, the tools necessary to review this data (though not specified, most likely DICOM) are not widely available to the Review Staff.

#5 Electronic Submission Related Questions

5.4 Is the proposal for the Review and Archival Copies as stated in the Electronic Submission Proposal acceptable?

- Again, I would recommend eliminating paper wherever permitted, it is Center policy to, whenever possible, do its review work from the “archival” copy.
- Refer to the Guidance “Providing Regulatory Submissions in Electronic Format – NDAs” posted January 1999 as IT3.
- More specific comments to follow

NDA Electronic Submission Proposal

Unless specifically mentioned, all sections should be presumed acceptable when taken with the following comments.

Section 2.0 GENERAL DETAILS

- As mentioned previously, pay particular attention to the Guidance “Submitting Marketing Applications According to the ICH – CTD Format, General Considerations” posted 8/2001 pertaining to granularity and nomenclature conventions
- Limited Bookmarks and Hyperlinks in “Scan Assembled” pdf documents is understood, however, the ease and accuracy of review is somewhat dependant on the completeness of Bookmarks and Hyperlinks in order to find the appropriate data and wherever possible should be included.

NDA Electronic Submission Proposal

Unless specifically mentioned, all sections should be presumed acceptable when taken with the following comments.

Section 3.2.3 Synopsis of Individual Studies

- When documents (electronic) are called for in more than one location, it is not necessary (as you noted) to duplicate the file in all locations.
- It is helpful, however, to place a pdf file in the empty folder (with a hyperlink) that can direct a Reviewer to the populated folder. Many Reviewers now maneuver through electronic submissions at the folder level and this would alleviate possible confusion over the location of the data

NDA Electronic Submission Proposal

Unless specifically mentioned, all sections should be presumed acceptable when taken with the following comments.

Section 3.5.3 Case Report Tabulation Section

- The content of the CRT section(s) as SAS transport files meets Guidance specification.
- The actual data to be included is a Reviewer decision

The Division stated that programs files for AUC calculations and analyzing physical examination variables should be included in the NDA submission.

The meeting was adjourned at this time.

Post-meeting Notes

The Division provides the following additional information addressing question 4.1 from the Non-clinical related questions:

BIPI listed the following in the briefing package:

Module 4

4.2.3.7 Other Toxicity Studies

4.2.3.7.1 U97-2343 Toxicity Study in Mouse

4.2.3.7.2 U98-3066 Toxicity Study in Mouse

4.2.3.7.3 U03-xxxx 13-wk inhalation study in Wistar rats

The CTD calls for:

4.2.3.7 Other Toxicity Studies if Available

4.2.3.7.1 Antigenicity

4.2.3.7.2 Immunotoxicity

4.2.3.7.3 Mechanistic studies (if not include elsewhere)

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

/s/

Christine Yu
10/24/03 05:00:21 PM



IND 57,948

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

Attention: Theresa Maloney
Senior Associate Director, Drug Regulatory Affairs

Dear Ms. Maloney:

We refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Combivent Respimat (ipratropium bromide and albuterol sulfate (b) (4)).

We also refer to your September 21, 2001, request, serial number 013, for a special clinical protocol assessment, received September 24, 2001.

We have completed our review of your submission and, based on the information submitted, have the following responses to your questions. For ease of reference, the questions raised in your submission are printed in Italics below, followed by our responses.

- Does the Agency concur that the planned 3-month Phase III study (1012.46) with Combivent Respimat in COPD patients is sufficient for registration of the Combivent Respimat inhalation spray?*

This protocol addresses one of the suggested program elements mentioned in the 1994 Points To Consider (PTC), the Phase 3 efficacy study. The protocol for this study is generally acceptable, with one major exception; the trial does not include an ipratropium (alone) Respimat arm. (b) (4)

We suggest that the proposed trial include an ipratropium (alone) Respimat treatment arm. However, a separate study may also be performed to address the added benefit of the combination product over ipratropium alone.

We note that other elements in the PTC document include a dose-ranging study and the general requirement for long-term safety studies. We assume these elements will be otherwise met.

2.

[REDACTED] (b) (4)

The above question is beyond the scope of a Special Protocol Assessment request. It addresses overall drug development, which we could address in a different correspondence.

3.

[REDACTED] (b) (4)
?

The above question is beyond the scope of a Special Protocol Assessment request. It addresses overall drug development, which we could address in a different correspondence.

We also have the following additional comments.

4. Clarify the various classes of bronchodilators alluded to under the fourth element of the inclusion criteria [Page 18].
5. Inclusion criterion #4 enriches the patient sample by requiring both the use of bronchodilators and the symptom of bronchospasm [Page 18]. In so doing, it may in part select for misdiagnosed asthma patients. Eliminate inclusion criterion #4 and include diagnostic criteria for COPD patients. Patients seem to be eligible if they think they have the diagnosis, without any assurance that this diagnosis was the result of the usual stringent inclusive standards.
6. Clarify the referent of the superscript "4" in the table, "Permitted Medications and Medications Restrictions." The superscript has been defined but seems not to be associated with anything in the table in which it is used [Page 30].
7. Clarify how patients are managed between the Screening/Baseline visit #1 and visit #2 which occurs two weeks later [Pages 8 & 24].

8. Determine the primary efficacy endpoint at week 12 after dosing with the inhaler that had been in-use for the preceding four weeks rather than substituting a new inhaler. Life-of-device efficacy considerations mandate this [Pages 8 & 26].

If you wish to discuss our responses, you may request a meeting. Such a meeting will be categorized as a Type A meeting (refer to our draft “*Guidance for Industry; Formal Meetings With Sponsors and Applicants for PDUFA Products*”). Copies of the guidance are available through the Center for Drug Evaluation and Research from the Drug Information Branch, Division of Communications Management (HFD-210), 5600 Fishers Lane, Rockville, MD 20857, (301) 827-4573, or from the internet at <http://www.fda.gov/cder/guidance/index.htm>. This meeting would be limited to discussion of this protocol. If a revised protocol for special protocol assessment is submitted, it will constitute a new request under this program.

If you have any questions, call Ms. Ladan Jafari, Regulatory Project Manager, at 301-827-5584.

Sincerely,

{See appended electronic signature page}

Robert J. Meyer, M.D.
Director
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Robert Meyer
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