CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021747Orig1s000

CHEMISTRY REVIEW(S)

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

DATE: 26-Sep-2011

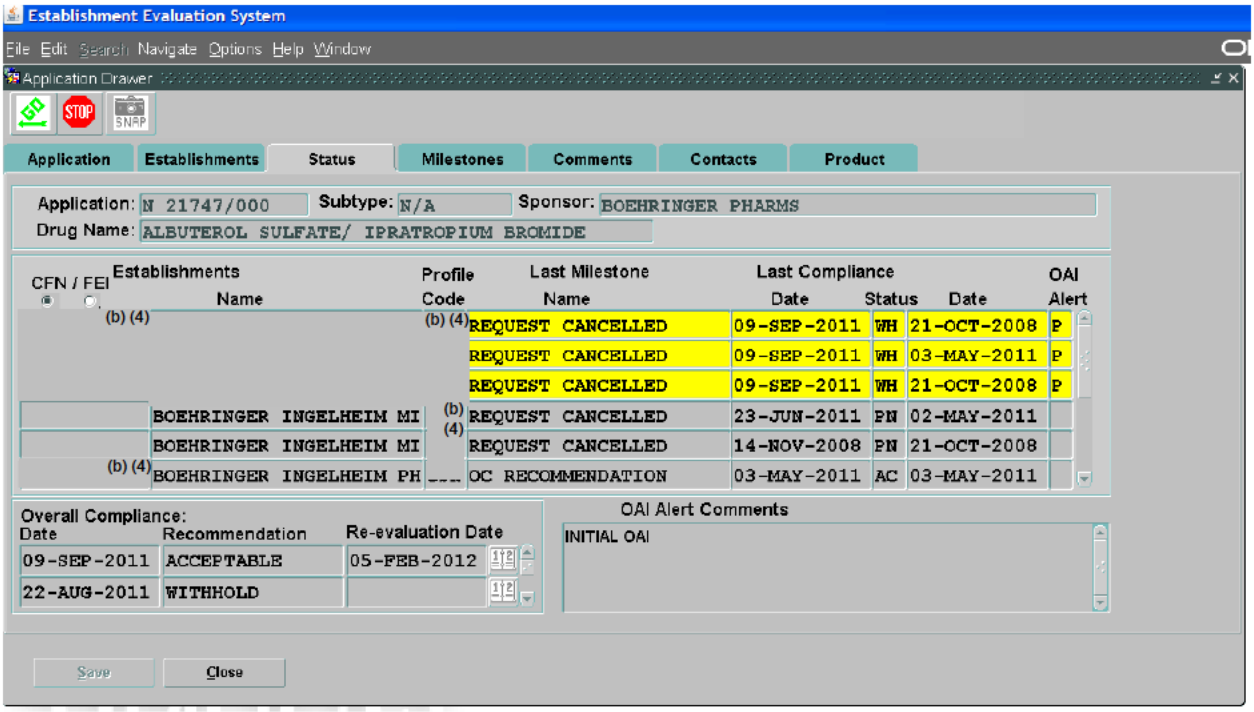
TO: N 21-747 File

FROM: Edwin Jao, Ph.D.
Chemistry Reviewer
ONDQA, Division III, Branch VII

SUBJECT: Recommendation for approval from CMC perspective based on the "Acceptable" recommendation from the Office of Compliance

Summary and Conclusion:
NDA 21747 was recommended for "Complete Response" from CMC perspective due to the "Withhold" recommendation from the Office of Compliance (see review by Edwin Jao, dated 8/26/2011). The office of Compliance issued an "Acceptable" recommendation on 9/9/2011. There are no other pending CMC issues. This submission is now recommended for approval from CMC perspective.

Attachment: EES Status



Appears This Way in Original

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

/s/

EDWIN JAO
09/26/2011

PRASAD PERI
09/26/2011
I concur

Chemistry Review Data Sheet

NDA 21-747

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

Boehringer Ingelheim Pharmaceuticscals, Inc.

Chemistry Review #2

Date: August 4, 2011

Recommendation: Approval

Edwin Jao, Ph.D.
ONDQA/Division III/Branch VII

Reference ID: 3007152

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Chemistry Assessment **15**

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Chemistry Review Data Sheet

1. NDA 21-747

2. REVIEW #: 2

3. REVIEW DATE: August 26, 2011

4. REVIEWER: Edwin Jao, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original NDA	October 7, 2008

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
resubmission	April 8, 2011

7. NAME & ADDRESS OF APPLICANT:

Name:	Boehringer Ingelheim Pharmaceuticals, Inc.
Address:	900 Ridgebury Rd./P.O. Box 368 Ridgefield, CT 06877-0368
Representative:	Amy Van Andel, DVM, MPH Senior Associate Director, Drug Regulatory Affairs
Telephone:	203-798-5452

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8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Combivent Respimat
b) Non-Proprietary Name (USAN): ipratropium bromide and albuterol sulfate inhalation spray
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: anticholinergic (ipratropium) and beta-adrenergic (albuterol)

11. DOSAGE FORM: spray, metered

12. STRENGTH/POTENCY: delivered from the actuator (per inhalation): 20 mcg ipratropium bromide monohydrate and 100 mcg albuterol (equal to 120 mcg albuterol sulfate). One actuation equals one dose.

13. ROUTE OF ADMINISTRATION: respiratory (inhalation)

14. Rx/OTC DISPENSED: __x_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___x___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Ipratropium Bromide:

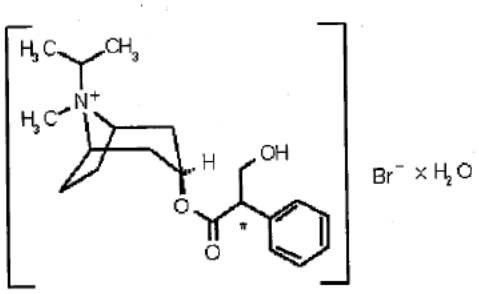
Ipratropium bromide (SCH 1000 BR)

Reference ID: 3007152

(8r)-3-alpha-Hydroxy-8-isopropyl-1-alpha-H,5-alpha-H-tropanium bromide (±)-tropate

Molecular weight: 430.4
CAS Number: 66985-17-9
$C_{20}H_{30}BrN0_3 . H_20$

Structural formula



Albuterol Sulfate:

Salbutamol Sulphate/A1buterol Sulfate (USP)

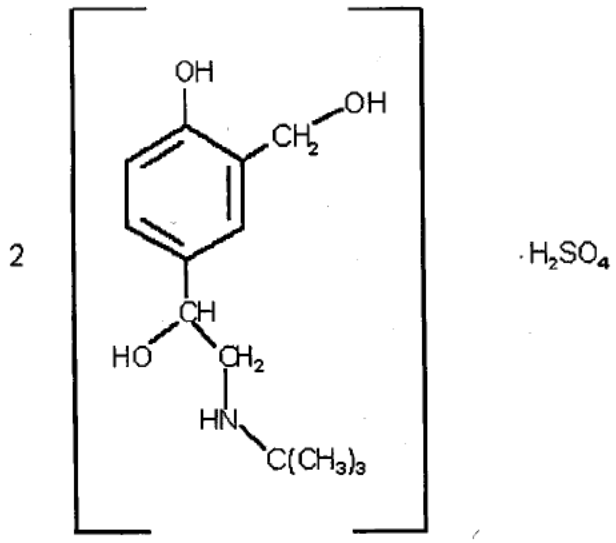
(RS)-2-tert-Butylamino-1-[4-hydroxy-3-(hydroxymethyl)phenyl)]-ethanolsulfate (Ph.Eur.)

1,3-Benzenedimethanol, alpha[1] –[[(1, 1-dimethylethyl)amino]methyl]-4-hydroxy-, sulfate (2:1) (salt) (USP)
Molecular weight: 576.7
CAS Number: 51022-70-9
$C_{26}H_{44}N_2\ 0_{10}\ S$

Reference ID: 3007152

Chemistry Review Data Sheet

Structural formula



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)		1	Adequate	NAI review with comments 01/23/2009 3 NAI reviews (6/16/2011) for annual reports 7 and 8 (9/14/09 and 10/8/10), respectively), and amendment dated 8/12/09 by Dr. Alan Schroeder	LOA date 8/30/2007
(b) (4)	II			1	Adequate	04/24/2009 (CMC) NAI reviews dated	LOA date 12/08/2006

Reference ID: 3007152

(b) (4)			6/17/11 for Annual reports #7 (9/14/09) and #8 (10/08/2010) by Dr. Alan Schroeder. NAI with comments by Dr. Edwin Jao (8/25/11) for amendment dated 8/12/2009	
	1	Adequate	Jan. 13, 2009: two reviews: NAI with comments, and NAI with no comments. Amendment (7/1/2008), Annual Reports 5, 6, 7 (dated 3/24/09, 3/29/10, and 3/24/11, respectively) NAI on 6/17/11 (with comments) by Dr. Alan Schroeder	LOA date 5/20/2005
	1	Adequate (and supporting DMFs are adequate)	NAI for Annual reports 7 (4/12/10) and 8 (4/4/11); NAI with comments for Amendments (1/07/10 and 6/6/11); all completed by Dr. Schroeder	LOA date 9/04/2008

Reference ID: 3007152

						on 7/7/2011; NAI for Supporting DMF (b) (4) Annual Report (3/30/11), completed on 7/7/11, amendment (2/23/11) completed on 6/24/11; NAI for Supporting DMF (b) (4) Annual report (12/18/08), completed on 2/27/09, all by Dr. Schroeder. Supporting DMF (b) (4) reviewed on 6/30/2011 by Dr. Schroeder	
(b) (4)				1	Adequate	Annual reports 4 (5/11/09), 5 (5/11/10), and 6 96/07/11), Amendment dated 10/28/09 Reviewed by Dr. Edwin Jao on 8/25/2011	LOA date 8/29/2008
				1	Adequate	NAI for Annual reports 1 (9/9/2009) and 2 (10/22/2010) By Dr. Edwin Jao on 8/25/2011	LOA date – 3/31/2009
				1	Adequate	8/25/2011 by Dr. Edwin Jao	LOA date 10/30/2008

Reference ID: 3007152

Chemistry Review Data Sheet

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

Note that several of the above DMFs contain LOAs for supporting DMFs: these include the following: DMF (b) (4). This may not be a complete list as it was derived for DMFs that were reviewed for this NDA. See the individual DMF reviews for information pertaining to the supporting DMFs.

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	57,948	Combivent Respimat
NDA	(b) (4)	(b) (4)
NDA	20-291	Combivent Inhalation Aerosol
NDA	21-527	Atrovent HFA Inhalation Aerosol
NDA	19-085	Atrovent Inhalation Aerosol

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	consult not necessary		
EES	withhold	22-Aug-2011	
Pharm/Tox	No safety concerns per Review #1 by Dr. Alan Schroeder		
Biopharm	consult not necessary		
LNC	consult not necessary		

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Chemistry Review Data Sheet

Methods Validation	methods validation not recommended – see Review #1 by Dr. Alan Schroeder		
DDMAC & DMEPA	submitted by clinical Project Manager		
EA	Categorical exclusion accepted, see Review #1 by Dr. Alan Schroeder		
Microbiology	approval	Jun-24-2009	Dr. Bryans Riley

Radiopharmaceutical	[not applicable]		

Reference ID: 3007152

The Chemistry Review for NDA 21-747

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Complete Response due to "**Withhold**" recommendation from the Office of Compliance on 8/22/2011

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

No

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

There has been no change in the drug substance, drug product, and container/closure system since the original NDA submission. The following descriptions are duplicated from the 1st cycle review by Dr. Alan Schroeder:

This NDA for Combivent Respimat (ipratropium bromide and albuterol sulfate inhalation spray) is (b) (4), an inhalation spray (b) (4). The Respimat device is "a cylindrical shaped plastic inhalation device with a gray colored body and a clear base." The inhaler contains an orange colored cap. The cartridge is "an aluminum cylinder with a tamper protection seal on the cap." Prior to using the product for the first time, the patient inserts the cartridge into the inhaler device. The drug product must not be subject to freezing conditions, since they will damage the cartridge. One actuation of Combivent Respimat *delivers from the mouthpiece* "20 µg ipratropium bromide monohydrate and 100 µg albuterol (equivalent to 120 µg albuterol sulfate) per actuation from the mouthpiece. The delivered volume (of a single actuation) is given as 11.4 mcL. A dose consists of a single actuation. The drug product is labeled with 120 actuations for commercial samples and 60 actuations for physician samples. It is disposed after use with one cartridge." The mean metered volume (pump delivery) was determined to be (b) (4) which is the mean of the first and last (b) (4) actuations. (b) (4). The minimum fill of the reservoir during manufacturing is (b) (4) This represents an overfill of about (b) (4). This (b) (4) overfill is not available to the patient since the device locks after approximately 120 actuations are dispensed. The Respimat device contains an actuation counter. The drug product

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produces an aerosol by mechanical means; there is no propellant. The drug product must be primed before its first use, and reprimed if not used for specified intervals; this is described in the draft labeling. (b) (4)

The drug formulation is an aqueous solution, packaged in (b) (4) aluminum can (b) (4) designated as the "cartridge."). The solution formulation contains, in addition to the two drug substances, water for injection, (b) (4) hydrochloric acid, benzalkonium chloride, and EDTA (edetate disodium). (b) (4)

.

(b) (4)

(b) (4)

The maximum in use period claimed is 3 months.

Both drug substances, albuterol sulfate and ipratropium bromide monohydrate "are well known and FDA approved as components of Combivent Inhalation Aerosol (NDA 20-291)." Solid state characteristics of the drug substances are not critical for the drug product since the formulation is a solution.

B. Description of How the Drug Product is Intended to be Used

There has been no change in "How the drug product is intended to be used" since the original MDA submission. The following descriptions are duplicated from the 1st cycle

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review by Dr. Alan Schroeder, with the exception that the available long term stability data has been updated to 36 months.

The patient inserts the canister containing the formulation into the Respimat device, which meters the formulation and produces the aerosol spray, and then the patient replaces the transparent case bottom of the device. This is performed just before the first use of the product. The patient is not supposed to remove the cartridge from the Respimat device after this point, and this is indicated in the patient's labeling.

The drug product is primed before first use by actuating it until a spray is visible, and then actuating it three more times. If the product is not used for more than 3 days, it is reprimed by releasing one actuation. If the product is not used for more than 21 days, it is reprimed by following the initial priming instructions.

To use the product, it is held upright and the clear base is turned in the direction of the red arrows on the label until it clicks (one-half turn). Then the orange cap is opened, the patient breathes out, and seals his/her lips around the end of the mouthpiece and actuates the product by pressing the dose release button while breathing in slowly and deeply. The mouthpiece of the inhaler and the metal piece inside the mouthpiece are to be cleaned weekly by wiping with a damp cloth or tissue.

A single dose of drug product is one inhalation ex-mouthpiece. Combivent® Respimat® Inhalation Spray has been developed for oral inhalation for use in patients with chronic obstructive pulmonary disease (COPD) on a regular aerosol bronchodilator who continue to have evidence of bronchospasm and who require a second bronchodilator.

The long-term storage conditions are 25°C/60 % r.h. and the accelerated storage conditions are 40°C/75 % r.h. Six months of accelerated stability data are provided for both the primary and supporting stability studies. The drug product will also be labeled with the warning "avoid freezing" to avoid damaging the cartridge.

Stability data are available through *36 months* for the primary stability batches and 24 months for the supportive batches respectively under long-term storage conditions (25°C/60 % r.h.) and 6 months each under accelerated storage conditions (40°C/75 % r.h.). The proposed shelf life of 36 months is granted based on these data. The maximum in-use life of the product (after the cartridge is inserted into the Respimat device) is 3 months, and this is supported by in-use stability data.

It is physically possible to remove or switch cartridges in the Respimat device, however, this is not permitted by the labeling, and the drug product does lock after the labeled number of doses, therefore this puts an absolute limit on a patient trying to reuse the device with another cartridge.

C. Basis for Approvability or Not-Approval Recommendation

Reference ID: 3007152

- *All deficiencies listed in the CR letter, including the comments pertinent to labeling, have been satisfactorily addressed in the resubmission.*
- *The resubmission received an overall recommendation of **Withhold** from the Office of Compliance on 8/22/2001, due to significant GMP violations from the drug substance testing site Labor L & S.*
- *No change is made in the drug substance, drug product and device, compared to the original NDA..*
- *No change is made in the manufacturer, manufacturing process, and site for the drug substances and drug product, compared to the original NDA..*
- *A minor change is reported in testing sites (removal of (b) (4) for microbiological testing of the drug substances). EES requests have been updated (Ms. Patwardhan).*
- *All DMF updates have been reviewed. No significant issues have been identified. An IR letter for DMF (b) (4) was sent on 6/30/2011 (Dr. Schroeder). The response to the IR is not yet received. However, the information requested in the letter is not an approvability issue of the NDA.*
- *The proposed changes in microbial testing of the drug substance ipratropium bromide are considered acceptable by microbiologist Dr. Jim McVey.*
- *Stability data (both solution and performance) through 36 months is provided for three registration batches. No change is made in the acceptance criteria and testing methods. The proposed shelf life of 36 months, including 3 months of in-use period, is granted based on the satisfactory stability data.*

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Edwin, Ph.D./Date: August 10, 2010
Prasad Peri, Ph.D.
Sadaf Nabavian /

C. CC Block

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Reference ID: 3007152

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/s/

EDWIN JAO
08/26/2011

PRASAD PERI
08/26/2011
I concur

Chemistry Review Data Sheet

NDA 21-747

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

Boehringer Ingelheim Pharmaceuticals, Inc.

Chemistry Review #1

Date: June 4, 2009

Recommendation: Approvable

Alan C. Schroeder, Ph.D.
ONDQA/Division I/Branch II
for the Division of Pulmonary and Allergy Products

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Chemistry Review Data Sheet

1. NDA 21-747

2. REVIEW #: 1

3. REVIEW DATE: June 4, 2009

4. REVIEWER: Alan C. Schroeder, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original NDA	October 7, 2008
Amendment (BC)	November 14, 2008
Amendment (BC)	January 6, 2009
Amendment (BC)	February 17, 2009
Amendment (BC)	February 23, 2009
Amendment (BC)	April 3, 2009
Amendment (BC)	May 19, 2009

7. NAME & ADDRESS OF APPLICANT:

Name: Boehringer Ingelheim Pharmaceuticals, Inc.

Chemistry Review Data Sheet

Address:	900 Ridgebury Rd./P.O. Box 368 Ridgefield, CT 06877-0368
Representative:	Amy Van Andel, DVM, MPH Senior Associate Director, Drug Regulatory Affairs
Telephone:	203-798-5452

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Combivent Respimat
b) Non-Proprietary Name (USAN): ipratropium bromide and albuterol sulfate inhalation spray
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: anticholinergic (ipratropium) and beta-adrenergic (albuterol)

11. DOSAGE FORM: spray, metered

12. STRENGTH/POTENCY: delivered from the actuator (per inhalation): 20 mcg ipratropium bromide monohydrate and 100 mcg albuterol (equal to 120 mcg albuterol sulfate). One actuation equals one dose.

13. ROUTE OF ADMINISTRATION: respiratory (inhalation)

14. Rx/OTC DISPENSED: __x_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___x___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

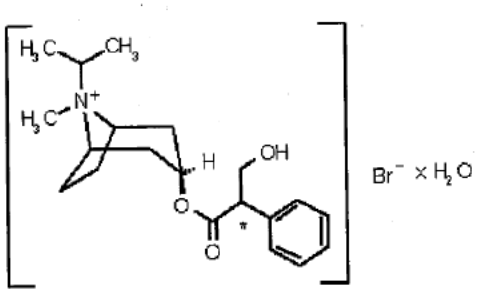
Ipratropium Bromide:

Ipratropium bromide (SCH 1000 BR)

(8r)-3-alpha-Hydroxy-8-isopropyl-1-alpha-H,5-alpha-H-tropanium bromide (±)-tropate

Molecular weight: 430.4
CAS Number: 66985-17-9
$C_{20}H_{30}BrN0_3 \cdot H_20$

Structural formula



Albuterol Sulfate:

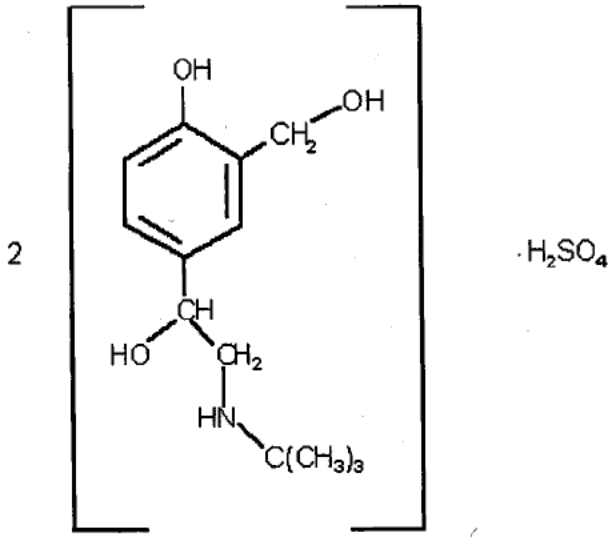
Salbutamol Sulphate/A1buterol Sulfate (USP)

(RS)-2-tert-Butylamino-1-[4-hydroxy-3-(hydroxymethyl)phenyl)]-ethanolsulfate (Ph.Eur.)

1,3-Benzenedimethanol, alpha[1] –[[(1, 1-dimethylethyl)amino]methyl]-4-hydroxy-, sulfate (2:1) (salt) (USP)
Molecular weight: 576.7
CAS Number: 51022-70-9
$C_{26}H_{44}N_2\ 0_{10}\ S$

Chemistry Review Data Sheet

Structural formula



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	Adequate	NAI review with comments 01/23/2009	LOA date 8/30/2007
	II			1	Adequate for CMC (micro. aspects to be eval. separately)	04/24/2009 (CMC)	LOA date 12/08/2006
	III			1	Adequate	Jan. 13, 2009: two reviews: NAI with comments, and NAI with no comments.	LOA date 5/20/2005
	III			1	Adequate (and supporting	2/27/09	LOA date 9/04/2008

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(b) (4)		(b) (4)		DMFs are adequate)		
	III		1	Adequate	2/25/09	LOA date 8/29/2008
	III		1	Adequate for CMC (micro. aspects to be eval. separately)	5/15/2009 (CMC)	LOA date – 3/31/2009

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

Note that several of the above DMFs contain LOAs for supporting DMFs: these include the following: DMF (b) (4). This may not be a complete list as it was derived for DMFs that were reviewed for this NDA. See the individual DMF reviews for information pertaining to the supporting DMFs.

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	57,948	Combivent Respimat
NDA	(b) (4)	(b) (4)
NDA	20-291	Combivent Inhalation Aerosol
NDA	21-527	Atrovent HFA Inhalation Aerosol
NDA	19-085	Atrovent Inhalation Aerosol

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	consult not necessary		

Chemistry Review Data Sheet

EES	[evaluations still pending – some inspections are scheduled for late May 2009]	[submitted by Prasad Peri, Oct/Nov 2008]	
Pharm/Tox	No safety concerns	March 31, 2009	Luqi Pei, Ph.D.
Biopharm	consult not necessary		
LNC	consult not necessary		
Methods Validation	methods validation not recommended – see this review		
DDMAC & DMEPA	submitted by clinical Project Manager		
EA	Categorical exclusion accepted	(in this review)	
Microbiology	pending	Submitted Nov. 14, 2008	

Radiopharmaceutical	[not applicable]		

The Chemistry Review for NDA 21-747

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approvable pending satisfactory compliance recommendation for the manufacturing and testing facilities to be used, pending satisfactory microbiology consult reviews of NDA and two supporting DMFs and pending satisfactory responses to the requests for clarifications at the end of this review (prior to the attachments).

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Agreement made for the next review cycle, prior to approval:

To provide in-use stability data for the drug product using drug product stored for 23 months under the long term storage condition. Cartridges are to be inserted into the inhaler and stored up to 3 months to cover the maximum in use period.

Post-approval agreements made by the applicant are listed below:

The applicant has agreed:

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. To provide the updated specification documents (including methods) as soon as they are available as an amendment to the NDA (if filed during the review cycle) or as general correspondence.

e. to revisit the extractable specifications for the Respimat (device) components after 1 year (estimated 10 inhaler batches).

f. to revisit the extractable specifications for the cartridge container components after 1 year (approximately 10 container and cap batches).

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

This NDA for Combivent Respimat (ipratropium bromide and albuterol sulfate inhalation spray) (b) (4), an inhalation spray (b) (4) The Respimat device is "a cylindrical shaped plastic inhalation device with a gray colored body and a clear base." The inhaler contains an orange colored cap. The cartridge is "an aluminum cylinder with a tamper protection seal on the cap." Prior to using the product for the first time, the patient inserts the cartridge into the inhaler device. The drug product must not be subject to freezing conditions, since they will damage the cartridge. One actuation of Combivent Respimat *delivers from the mouthpiece* "20 µg ipratropium bromide monohydrate and 100 µg albuterol (equivalent to 120 µg albuterol sulfate) per actuation from the mouthpiece. The delivered volume (of a single actuation) is given as 11.4 mcL. A dose consists of a single actuation. The drug product is labeled with 120 actuations for commercial samples and 60 actuations for physician samples. It is disposed after use with one cartridge." The mean metered volume (pump delivery) was determined to be (b) (4) which is the mean of the first and last (b) (4) actuations. (b) (4) The minimum fill of the reservoir during manufacturing is (b) (4) This represents an overfill of about (b) (4). This (b) (4) overfill is not available to the patient since the device locks after approximately 120 actuations are dispensed. The Respimat device contains an actuation counter. The drug product produces an aerosol by mechanical means; there is no propellant. The drug product must be primed before its first use, and reprimed if not used for specified intervals; this is described in the draft labeling. (b) (4)

The drug formulation is an aqueous solution, packaged in (b) (4) an aluminum can (b) (4) designated as the "cartridge."). The solution formulation contains, in addition to the two drug

substances, water for injection, (b) (4) hydrochloric acid, benzalkonium chloride, and EDTA (edetate disodium). (b) (4)

(b) (4)

.

(b) (4)

The maximum in use period claimed is 3 months.

Both drug substances, albuterol sulfate and ipratropium bromide monohydrate "are well known and FDA approved as components of Combivent Inhalation Aerosol (NDA 20-291)." Solid state characteristics of the drug substances are not critical for the drug product since the formulation is a solution.

B. Description of How the Drug Product is Intended to be Used

The patient inserts the canister containing the formulation into the Respimat device, which meters the formulation and produces the aerosol spray, and then the patient replaces the transparent case bottom of the device. This is performed just before the first use of the product. The patient is not supposed to remove the cartridge from the Respimat device after this point, and this is indicated in the patient's labeling.

The drug product is primed before first use by actuating it until a spray is visible, and then actuating it three more times. If the product is not used for more than 3 days, it is reprimed by releasing one actuation. If the product is not used for more than 21 days, it is reprimed by following the initial priming instructions.

To use the product, it is held upright and the clear base is turned in the direction of the red arrows on the label until it clicks (one-half turn). Then the orange cap is opened, the patient breathes out, and seals his/her lips around the end of the mouthpiece and actuates the product by pressing the dose release button while breathing in slowly and deeply. The mouthpiece of the inhaler and the metal piece inside the mouthpiece are to be cleaned weekly by wiping with a damp cloth or tissue.

A single dose of drug product is one inhalation ex-mouthpiece. Combivent® Respimat® Inhalation Spray has been developed for oral inhalation for use in patients with chronic obstructive pulmonary disease (COPD) on a regular aerosol bronchodilator who continue to have evidence of bronchospasm and who require a second bronchodilator.

Based on the stability data, the applicant has proposed a (b) (4) expiration dating period at 25°C (77°F) with excursions permitted to 15-30°C (59-86°F). The expiration dating period to be granted, however, based upon the data, is (b) (4) as discussed in this review. The stability data include 12 months of long term primary stability data for the proposed commercial drug product, and 24 months of supporting long-term stability data (the supporting data are from stability batches which use the Respimat A4 device and a formulation in which the active ingredients have (b) (4) as for the proposed commercial drug product). The long-term storage conditions are 25°C/60 % r.h. and the accelerated storage conditions are 40°C/75 % r.h. Six months of accelerated stability data are provided for both the primary and supporting stability studies. The drug product will also be labeled with the warning "avoid freezing" to avoid damaging the cartridge.

Stability data are available through 12 months for the primary stability batches and 24 months for the supportive batches respectively under long-term storage conditions (25°C/60 % r.h.) and 6 months each under accelerated storage conditions (40°C/75 % r.h.). The maximum in-use life of the product (after the cartridge is inserted into the Respimat device) is 3 months, and this is supported by in-use stability data.

It is physically possible to remove or switch cartridges in the Respimat device, however, this is not permitted by the labeling, and the drug product does lock after the labeled number of doses, therefore this puts an absolute limit on a patient trying to reuse the device with another cartridge.

C. Basis for Approvability or Not-Approval Recommendation

Recommendation is approvable pending satisfactory compliance recommendation for the manufacturing and testing facilities to be used, pending satisfactory microbiology consult reviews of NDA and two supporting DMFs and pending satisfactory responses to the requests for clarifications at the end of this review (prior to the attachments).

Manufacturing and control information for the drug substances is referred to the Type II DMFs (b) (4) (The DMF holder is (b) (4) . These two DMFs have both been found to be adequate for CMC. Separate

microbiological reviews of appropriate microbiological aspects of this NDA and DMF (b) (4) and DMF (b) (4) (for the plastic container for Respimat) are pending.

CDRH has provided a consult review of the Respimat device (b) (4) This review is included in a review of the device DMF (b) (4) The manufacturing and controls of the device were previously found to be adequate by CDRH. Since the drug product (cartridge) is manufactured (b) (4) the microbiology group in OPS has been requested to provide a consult review of the microbiological aspects of the drug product and the manufacturing process of the filled cartridge. This will be provided in separate review documents. The review pharmacologist has provided a consult review of the drug product for a safety review of drug related impurities, degradation products, leachables, foreign particulates, and the benzalkonium chloride and disodium edetate excipients. No nonclinical safety concerns were found.

There have been multiple versions of the Respimat inhaler during the development of this ipratropium bromide and albuterol sulfate inhalation spray drug product. The applicant has (b) (4) stated (b) (4) that the basic operating principles of the device (for dosing and aerosolization) were not changed over the development process. Three inhaler versions were used in the development of Combivent Respimat: Respimat A3 (for clinical phase 2 studies), Respimat A4 (for drug product characterization studies and for supportive stability batches) and Respimat A5 (for phase 3 clinical supplies and for primary stability batches). (b) (4)

The stability data, which are limited to 12 months long term data in the original NDA, and the supportive stability data (which are through 24 months) support an expiration dating period for the drug product of (b) (4) The in use stability data support an in-use period of three months for the drug product in which the cartridge has been inserted into the device.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Alan C. Schroeder, Ph.D./Date: June 4, 2009
Ali Al-Hakim, Ph.D./
Sadaf Nabavian /

C. CC Block

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

/s/

Alan Schroeder
6/10/2009 05:44:25 PM
CHEMIST

Ali Al-Hakim
6/10/2009 05:48:42 PM
CHEMIST

NDA 21-747
Combivent Respimat
(ipratropium bromide and albuterol sulfate) Inhalation Spray

Summary of the Basis for the Recommended Action from Chemistry, Manufacturing, and Controls

Applicant: Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Rd./P.O. Box 368
Ridgefield, CT 06877-0368

Indication: Patients with chronic obstructive pulmonary disease (COPD) on a regular aerosol bronchodilator who continue to have evidence of bronchospasm and who require a second bronchodilator.

Presentation: the drug product, Combivent Respimat, is delivered through an inhaler device. One actuation of Combivent Respimat *delivers from the mouthpiece* 20 µg ipratropium bromide monohydrate and 100 µg albuterol (equivalent to 120 µg albuterol sulfate) per actuation from the mouthpiece. The delivered volume (of a single actuation) is given as 11.4 mcL. A dose consists of a single actuation. The drug formulation is an aqueous solution, packaged in (b) (4) an aluminum can (b) (4) designated as the "cartridge."). The cartridge is inserted into the Combivent inhaler (device) prior to the first use by the patient.

EER Status:	Recommendations:	Pending
Consults:	EA –	Categorical exclusion provided & accepted
	CDRH-	N/A (the device was reviewed by CDRH as a consult (b) (4) (b) (4)
	Statistics –	N/A
	Methods Validation –	Not recommended
	Biopharm–	N/A
	Microbiology –	Recommend Approval (6/22/2009)
	Pharm/toxicology –	Acceptable (3/31/2009)

Original Submission: 07-October-2008
Re-submissions: N/A

Post-Approval CMC Commitments:

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. To provide the updated specification documents (including methods) as soon as they are available as an amendment to the NDA (if filed during the review cycle) or as general correspondence.
e. To revisit the extractable specifications for the Respimat (device) components after 1 year (estimated 10 inhaler batches).
f. To revisit the extractable specifications for the cartridge container components after 1 year (approximately 10 container and cap batches).

Background:

This NDA is submitted under 505(b)(1). The NDA for Combivent Respimat (ipratropium bromide and albuterol sulfate inhalation spray) is (b) (4) an inhalation spray ((b) (4)

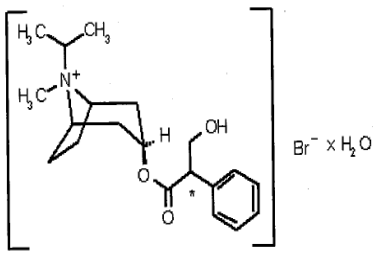
There have been multiple versions of the Respimat inhaler during the development of this ipratropium bromide and albuterol sulfate inhalation spray drug product. The applicant has (b) (4) stated ((b) (4) that the basic operating principles of the device (for dosing and aerosolization) were not changed over the development process.

Drug Substances:
There are two, non-novel drug substances: *ipratropium bromide monohydrate* and *albuterol sulfate*. These drug substances are well known and are indicated to have been approved as components of Combivent Inhalation Aerosol (NDA 20-291, a CFC MDI).

All of the information which pertains to these drug substances is cross referenced to DMF (b) (4) (albuterol sulfate) and DMF (b) (4) (ipratropium bromide). The CMC information for the drug substances in the corresponding DMFs was reviewed and found adequate.

Ipratropium bromide monohydrate
The ipratropium bromide is a quaternary ammonium compound and it is freely soluble in water (>90 mg/mL).
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT
Chemical Name
(8r)-3-alpha-Hydroxy-8-isopropyl-1-alpha-H,5-alpha-H-tropanium bromide (±)-tropate

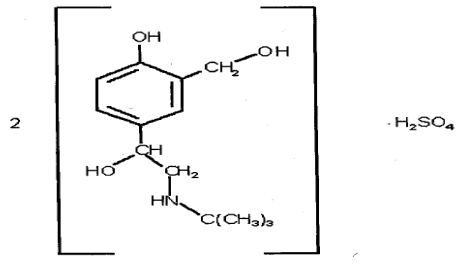
Structural formula



Molecular Weight: 430.4
Molecular Formula: :
$C_{20}H_{30}BrNO_3 . H_2O$

Salbutamol Sulphate/A1buterol Sulfate
Albuterol has two ionizable groups: the phenolic hydroxyl group (pKa = 9.3) and the secondary amine group (pKa 10.3). Therefore, albuterol is freely soluble in acidic aqueous solutions (approximately 200 mg/mL).
Chemical Name
(RS)-2-tert-Butylamino-1-[4-hydroxy-3-(hydroxymethyl)phenyl)]-ethanolsulfate

Structural formula



Molecular weight: 576.7
Molecular Formula: $C_{26}H_{44}N_20_{10}S$

Conclusion: The drug substances are satisfactory

Drug Product:
The drug product is described as being composed of a "sterile, aqueous, multi-dose solution of ipratropium bromide monohydrate and albuterol sulfate for oral inhalation delivered by the Respimat inhaler. Each actuation from the Respimat inhaler delivers 20 mcg of ipratropium bromide monohydrate and 100 mcg of albuterol in 11.4 mcL of solution from the inhaler mouthpiece. The recommended dose is 1 actuation 4 times a day." The device will only be used with a single cartridge; it is not refillable. The number of actuations on the label is 120 for the commercial product and 60 actuations for the physician's sample. Once the cartridge is inserted into the Respimat device, the drug product may be used for up to 3 months.

The drug formulation is an aqueous solution, packaged in (b) (4) an aluminum can or cylinder (cartridge). The solution formulation contains, in addition to the two drug substances, water for injection, (b) (4) hydrochloric acid, benzalkonium chloride, and EDTA (edetate disodium). (b) (4)

The provided stability data support an expiration dating period for the drug product of (b) (4) for the drug product.

The main outstanding CMC remaining issues related to the drug product include:

- **Potential leachable and malfunction issues for the device**
- **Modification of a specification for an alternate analytical method for aerodynamic particle size distribution**
- **Patient use issue pertaining to the insertion of the cartridge into the device**

Conclusion: The drug product is not satisfactory.

Overall Conclusion:
From a CMC perspective, the application is approvable pending satisfactory responses to the CMC deficiencies and acceptable cGMP recommendation from office of compliance.

Ali Al-Hakim, Ph.D.
Branch Chief,
DPA I/ONDQA

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 21747	ORIG 1		COMBIVENT RESPIMAT

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/s/

ALI H AL HAKIM
08/05/2009

OND Division of Pulmonary and Allergy Products

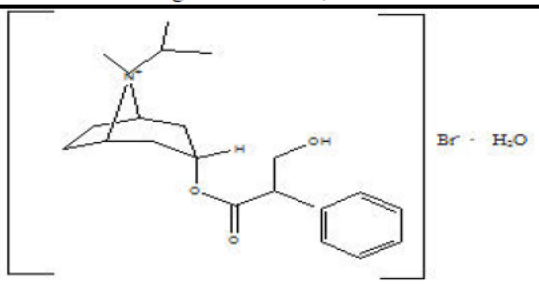
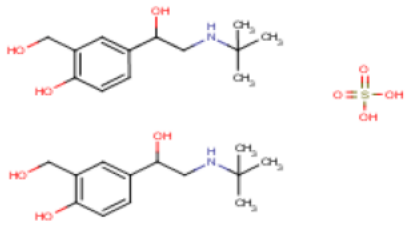
NDA: 21-747
Applicant: Boehringer Ingelheim
Stamp Date: 8-Oct-2008
PDUFA Date: 8-Aug-2009
Proposed Proprietary Name: Combivent® Respimat®
Established Name: ipratropium bromide and albuterol sulfate inhalation spray (combination of an anticholinergic and a beta-adrenergic)
Dosage form and strength: Inhalation Spray [redacted] each dose (1 actuation) delivers 20 mcg ipratropium bromide (monohydrate) and 100 mcg albuterol (equivalent to 120 mcg albuterol sulfate): corresponding to [redacted] ipratropium bromide (monohydrate) and [redacted] albuterol.
Route of Administration: Oral Inhalation
Indications: for use in patients with chronic obstructive pulmonary disease (COPD) on a regular aerosol bronchodilator who continue to have evidence of bronchospasm and who require a second bronchodilator.
Proposed Dose: One inhalation four times a day, not to exceed six inhalations in 24 hours.
PAL: Prasad Peri, Ph.D. Branch 2/DPA I/ONDQA
Fileability recommendation: Acceptable for filing
Review team recommendation: Primary reviewer: Alan Schroeder, Ph.D.
Time goals:

Initial Quality Assessment (Filing Date): by 7-Nov-2008 (Found acceptable for filing)
Chemistry filing memo in DFS: by 7-Nov-2007
Filing decision "Day 30 (early)": **7-Nov-2008** (30 days!)
74 Day letter Due: 22-Dec-2008 (tentative; to be set by Clinical Division)
Chemistry Review (DR/IR) letter: by 8-Mar-2009! (tentative)
Mid-cycle meeting "Month 5": 8-Mar-2009 (to be set by Clinical Division)
Advisory Committee Meeting: N/A
Full Labeling Meeting: ~ 11-May-2009
Wrap-up: ~8-Jun-2009
Labeling Tcon: ~16-Jun-2009
Final Chemistry Review "Month 8" in DFS: by 8-Jun-2008
PDUFA: 8-Aug-2009

Related Documents

INDs pertaining to this are: 57,948 (Combivent Respimat), IND 32,529 (Combivent Inhalation Aerosol (CFC), IND 45,938 (Atrovent HFA), [redacted] 46,687 (Spiriva Handihaler), IND [redacted] IND [redacted], NDA 20-291, 20527, NDA19-085, [redacted] NDA 21-395,

USAN/INN	Ipratropium Bromide
Chemical Name IUPAC	8-azoniabicyclo[3.2.1] octane, 3-(3-hydroxy-1-oxo-2-phenylpropoxy)-8-methyl-8-(1-methylethyl)-, bromide monohydrate, (3-endo, 8-syn)
CAS #	66985-17-9
Molecular Formula	$C_{20}H_{30}BrNO_3 \cdot H_2O$
Molecular weight	430.4

Structure	
USAN/INN	Albuterol Sulfate/Salbutamol Sulfate
Chemical Name IUPAC	1,3-Benzenedimethanol, alpha(sup 1)-(((1,1-dimethylethyl)amino)methyl)-4-hydroxy-, sulfate (2:1) (salt)
CAS #	51022-70-9
Molecular Formula	$(C_{13}H_{21}NO_3)_2 \bullet H_2SO_4$.
Molecular weight	576.7
Structure	

CONSULTS/ CMC RELATED REVIEWS	**COMMENT**
Clinical Pharm (BA/BE) - Dissolution	Not applicable
CDRH	(b) (4) Not necessary
EA	Applicant claims Combivent Respimat will be replacing Combivent CFC MDI.
EES	EES for all 4 sites listed were sent out on Oct. 2008. The drug substances site was found adequate based on profile.
DMETS/DDMAC	Consensus is pending. Dosage form is an Inhalation Spray.
Methods Validation	To be sent when appropriate if necessary.
Microbiology	To be sent for sterility validation and the evaluation of microbial limits.
Pharm/Tox	Consult to be sent for evaluation of safety of the proposed levels of impurities and degradants. Leachables of the mouthpiece need to be evaluated.
Biometrics	12 months stability data look robust enough to identify trends in the data and assess shelf life. Supportive stability data for 24 months is provided for a higher strength batch.

Summary:

- This is a standard 10 month NDA paper NDA in CTD format with electronic labeling provided in SPL format. There is a Quality Overall Summary (59 pages). This NDA is filed as a 505(b) 1 application.
- This is classified as a new dosage form as per Draft MaPP 7500.3 (3S).

Drug Substance

- The drug substance ipratropium Bromide monohydrate is referenced to (b) (4) Type II Drug Master File (DMF (b) (4)) that is also referenced for the approved NDA for Atrovent Inhalation Aerosol, Combivent Inhalation Aerosol (CFC), and Atrovent

Nasal Spray. This DMF was reviewed in support of these applications by Dr. Stuart Zimmermann in Feb 2008 and it was found to be adequate.

- The drug substance albuterol sulfate is referenced to a [redacted] Type II Drug Master File (DMF [redacted]) that is also referenced for the approved NDA for Combivent Inhalation Aerosol. This DMF was reviewed in support of these applications by Dr. Craig Bertha in 2004 and it was found to be adequate. Subsequent to Dr. Bertha's review, there have been two amendments and five annual reports to the DMF and this DMF will need review of these amendments and annual reports. The DMF refers to an [redacted] albuterol sulfate. This is of no consequence since both drug substances [redacted].

Drug Product

- The product Combivent® Respimat® consists of a sterile aqueous inhalation solution of ipratropium bromide monohydrate and albuterol sulfate in a cartridge and a Respimat® inhaler. The principle of the Respimat® inhaler is to meter a small volume of the inhalation solution and to press it through a nozzle [redacted] resulting in the aerosol spray which is inhaled by the patient. The cartridge with the inhalation solution and the Respimat® inhaler are supplied as two entities in one package. Prior to first use, the patient inserts the cartridge into the inhaler.
- The composition of the drug product is shown on the next page. The basic principle of the device is provided in the development pharmaceutics section in detail. In short, when the device is actuated, [redacted] The A4 and A5 versions of the devices have been used in one pivotal clinical study each and the to-be marketed device is the A5. The A5 device incorporates a lockout mechanism. The to-be-marketed version also incorporates an orange cap.
- The device has a sliding dose indicator that moves from the green zone to a red zone as the device is used. The dose indicator is combined with a locking mechanism that locks the Respimat® inhaler to prevent further use once the labeled number of [redacted] doses has been delivered. After locking it is no longer possible to turn the lower part of the inhaler, rendering the Respimat® inhaler unusable.
- The cartridge (reservoir) that contains the drug solution consists of [redacted] an aluminum cylinder [redacted] and a tamper protection seal. The patient inserts the cartridge into the Respimat® inhaler, [redacted]
- The cartridge should not be frozen, [redacted]. This is also stated on the label. The cartridge contains a minimum fill of [redacted]. As the declared number of 120 doses of 11.4 µl each (metered volume) corresponds to about [redacted] the cartridge comprises an over fill of approximately [redacted] Overfills are common to multi-dose inhalation products. [redacted] The locking mechanism of the Respimat® inhaler guarantees that the overfill cannot be extracted from the cartridge. Therefore, in contrast to pMDIs, the over fill is, not accessible to the patient.

- It was asked during the EoP2 meeting that BI should describe their understanding of the observed (b) (4) over the life of the product. From the current data, on the primary stability batches, there is a (b) (4) from beginning to end of the device (Table 6, QOS). The Division indicated that they 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.

Table 17: Critical Components of the Respimat® inhaler (including suppliers and related DMFs)

No.	Component	Function / Description	Material / type	Material supplier / DMF
				(b) (4)

- **Container closure system.**

See figures above.

CRITICAL ISSUES

- **Pharmaceutical development**

Although the drug product is (b) (4) is necessary for the stability of the drug product solution. All excipients used meet pharmacopial grade and stability of the solution and its compatibility with the cartridge and Respimat inhaler has been demonstrated. Drug product characterization studies for the following parameters are reported in the NDA. Note that as agreed to in the EoP2 meeting, these studies were performed using the 40/200 strength and the data are being extrapolated to the lower strength (20/100).

A) Priming / Repriming in Various Orientations / Effect of Resting Time
B) Temperature Cycling
C) Cleaning Instructions
D) Device Robustness
E) Effect of Dosing Orientation
F) Tail Off Characteristics
G) Plume geometry
H) (b) (4)
I) Stability of Primary (Unprotected) Package

- **Dose Dumping**

Not applicable.

- **Microbial Testing**

In addition to sterility testing of the unopened cartridge, the (b) (4) is also performed and validated to assure microbial control. The (b) (4) manufacturing process and the sterility validation of the manufacturing process needs to be evaluated by the microbiology staff.

- **In-process controls**

In-process controls include (b) (4)

- **Critical Quality Attributes/ Process parameters**

The applicant discusses two main headings under target product profile: "Stability of the Inhalation Solution" and "Performance of the Respimat Inhalation Spray." Under stability the critical quality attributes are listed as chemical purity, leachables, content of benzalkonium chloride, content of edetate disodium and microbial purity. Under performance heading the critical quality attributes are listed as delivered dose and aerodynamic particle size distribution (APSD).

(b) (4)

(b) (4)

The sponsor investigated the microbiological status of Combivent® Respimat® under realistic conditions of use. These need to be evaluated by the microbiological staff. Cartridges used by patients in the phase III clinical trials were investigated. They showed negligible microbiological burden (94.5% or 200 cartridges showed no viable microorganism. In a few cases contamination with *staphylococcus warneri* was observed which could be attributed to an artifact in the lab).

BI wants (b) (4)

This has to be evaluated based on characterization data of the drug product.

Functionality and in use studies indicate that the devices are fairly robust. Results from returns program indicated that the delivered dose and APSD were comparable to the release results (b) (4) (Table 6 of QOS). It is not clear if this trend is significant or just variability in the method for Assay.

In the Combivent® Respimat® clinical phase 3 trials 1012.46 and 1012.56 approximately 10,600 Respimat® A4 and A5 inhalers were used by patients. Only four out of 35 suspected malfunctioning inhalers could be confirmed as relevant in trial 1012.46. Corrective actions have been implemented to prevent the defects in future batches. This is confirmed in trial 1012.56 where no malfunctioning inhalers were reported.

- **Overage in the formulation.**

(b) (4). An over fill of (b) (4) is used during the manufacture of the cartridge. The sponsor claims unlike a MDI the over-fill is not available for the patient since the device locks out after 120 doses (120 actuations) for trade sample and 60 actuations for the physician sample.

- **Excipients from Animal Origin.**

None

- **OVIs in the drug Product**

(b) (4) is tested for and controlled.

- **Manufacturing differences between pilot and commercial scales.**

Cartridge design (b) (4) The changes did not influence the properties of the product, as indicated by unchanged batch release and stability data. [Note that the primary stability batches used (b) (4) (phase III trial 1012.56), whereas supportive stability batches used (b) (4) (phase III trial 1012.46).]

Being a novel device, the Respimat® was developed with several interim versions and was not available in its final version from the very beginning of the product development. For Combivent® Respimat®, two versions of the device are of importance:

- the Respimat® version A4 – it has been used in the Phase III clinical studies (1012.46), this batch was (b) (4) size (high strength: 40 mcg of ipratropioum bromide and 200 mcg of albuterol per actuation)
- the Respimat® version A5, which is intended for the commercial product; it has been used in primary stability studies and in phase 3 trial 1012.56, this batches included the final commercial scale of (b) (4)

The composition of the three primary stability batches is identical to the composition of the clinical trial supplies of phase 3 trial 1012.56 and the commercial product (b) (4) (b) (4) The locking mechanism has no influence on the inhaler performance. The Respimat® A5 inhaler is the final inhaler intended to be marketed

- **GMP status of the drug substance/drug product manufacturing sites.**

Both drug substance and drug products are manufactured at the (b) (4). Alternate sites (b) (4), are responsible for microbiological testing of the drug substance and drug product. Both sites are pending EES status. (b) (4) is an alternate drug product testing site and is responsible for testing drug product.

- **Safety of imprinting inks.**

Not applicable

- **Dissolution of the drug product.**

Not applicable

- **Degradation products:**

A scheme for the degradation pathway is provided below. The proposed levels of degradants (see Drug Product Specifications) are claimed to be qualified. These need to be assessed by pharmtox reviewers. A consult needs to be sent to the pharmacologist to evaluate the levels of proposed degradants in the drug product. (b) (4) The sponsor claims that the proposed specification limits for the individual degradation products do not raise any toxicological concerns. (b) (4) The proposed levels seem to be qualified from previous levels but will need the input of a pharmtox reviewer.

- **Extractables and Leachables in the Drug Product**

Leachables data have been generated by long-term stability studies. In the primary stability batches representing the commercial product, leachables were found only in levels (b) (4) (b) (4)

The sponsor indicates that (b) (4)

A risk assessment showed that there is no (b) (4) concern. (b) (4)

(b) (4)

Leachables levels are below (b) (4) at all time points. They do not show a trend over time.

A toxicological evaluation of the extractables and leachables is presented and discussed in the non-clinical overview (Module 2) of the NDA. (b) (4)

- **Sensitivity of product to moisture and light.**

Not applicable. The formulation is an aq. solution and in a sealed aluminum canister.

Shelf life of the drug product (proposed (b) (4)

The company applies for a shelf-life of (b) (4) at room temperature (25°C; excursions permitted to 15–30°C). This includes a maximum in-use period of 3 months. There is the label statement that the product should be protected from freezing. Note in-use study was performed on a drug product stored only at 9 months. The sponsor should be asked to update the in-use stability data for the drug product when stored at 21 months for a maximum shelf life of (b) (4)

- **Device testing**

The tests on the inhaler performance at (b) (4) include for example: **Spray testing**, **Delivered mass:** (b) (4), **Particle size distribution:** (b) (4)

Dose indicator/ locking-mechanism: (b) (4)

Function testing of (b) (4)

- **Bulk Drug Product Stability Packaging Data and Protocol**

None proposed

- **Drug Product Stability**

The applicant has shown that the drug product is quite stable for 12 months. Real time data for 3 batches using the A4 device (24 months of (b) (4) and 6 months (b) (4) of the 40/200 strength of IPB and Albuterol) and 3 batches using the A5 device (12 months of (b) (4) and 6 months (b) (4), for the 20/100 strength of IPB and Albuterol). (b) (4)

- **Analytical Methods**

(b) (4)

. **This needs**

to be further evaluated. This proposal for alternate APSD method was found acceptable (b) (4)

(b) (4)

- **Comparability Protocol**

None proposed.

- **Is this a combination drug product/reviewed by OCP?**

This is a combination drug product. (b) (4) no CDRH issues identified for its manufacturing and control, (b) (4) .

- **In-use stability period**

The in-use stability of the product with the cartridge inserted into the Respimat® inhaler has been investigated on samples of the 1st stability set. The chemical stability – it was investigated on aged batches at 9 months and the proposed in-use period is 3 months.

Table 10 Proposed regulatory specifications for Combivent® Respimat® Inhalation Spray.

Test parameter	Analytical procedure (method no.)	Acceptance criteria
Appearance	(b) (4)	
Color of solution		
Clarity of solution		
pH		
Volume of contents		

Loss of mass	(b) (4)
Identification	(b) (4)
Active ingredient content	(b) (4)

Table 10 (cont'd) Proposed regulatory specifications (contd.)

Test parameter	Analytical procedure (method no.)	Acceptance criteria
Content of disodium edetate	(b) (4)	
Content of benzalkonium chloride		
Particulate matter		
Sterility		
Spray Content Uniformity (SCU)		
Pump delivery		
Number of actuations		

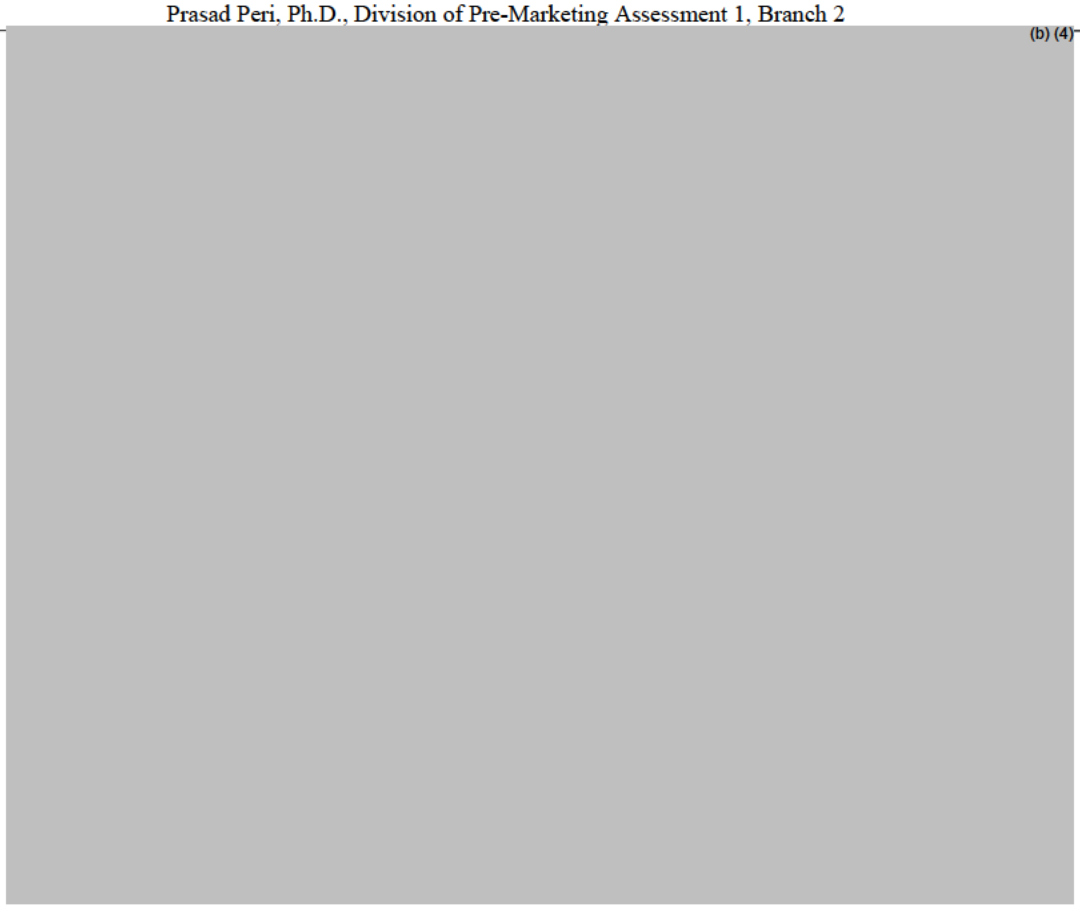


Figure 7 Decomposition pathways of albuterol in aqueous solution.

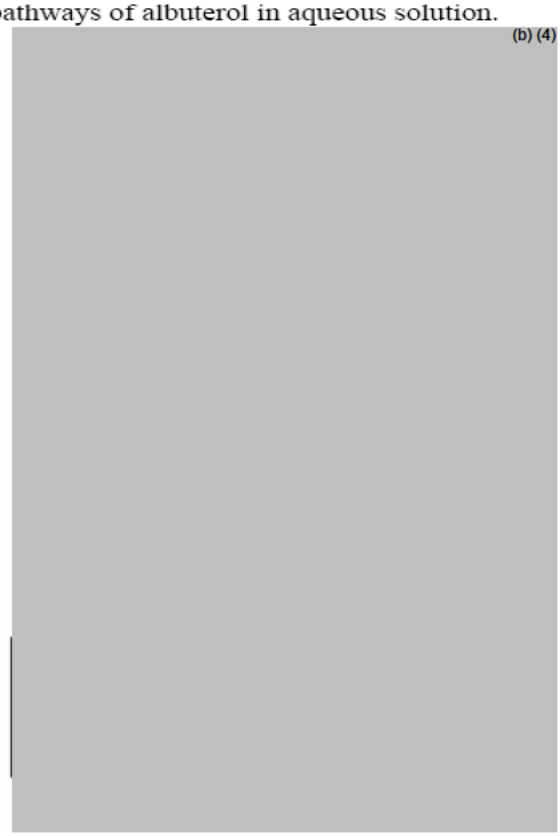


Figure 6 Decomposition pathways of ipratropium bromide in aqueous solution.

Table 10 (cont'd) Proposed regulatory specifications (contd.)

Test parameter	Analytical procedure [method number]	Acceptance criteria
Aerodynamic Particle Size Distribution (APSD)	(b) (4)	

Table 12 Critical Components of the Respimat® inhaler (including suppliers and related DMFs)

No.	Component	Function / description	Material / type	Material supplier / DMF
(b) (4)				

Table 13 Overview of primary and supportive stability batches

Batch number of Respimat® cartridge/ inhaler batch	Batch size (L)	(b) (4)	Respimat version no.	Date of cartridge manufacture	Available stability data (months)
Primary stability	**20 / 100 µg dose**				
701505/5U0007		(b) (4)	A 5	Jan 17, 2007	
701506/6L0038			A 5	Jan 22, 2007	12
701507/6L0043			A 5	Jan 31, 2007	
Supportive stability	**40 / 200 µg dose**				
203156/ WE 01080199		(b) (4)	A 4	April 29, 2002	
203157/ WE 02060127			A 4	May 6, 2002	24
204309/ WE 01070187			A 4	May 21, 2002	

DMF	Type	DMF Holder	Content	Comments
			(b) (4)	Last reviewed in 2004 for the same dosage form by Dr. Craig Bertha. Two amendments need to be reviewed.
				Last reviewed by Dr. Stuart Zimmermann in Feb 2008. Review of Updates
				Last reviewed (7/28/2008) by Dr. Alan Schroeder. IR sent.
				Last reviewed (7/14/2008) by Dr. Alan Schroeder. IR sent. Response dated 8/29/08 to be reviewed.
				Last reviewed (7/28/2008) by Dr. Alan Schroeder. IR sent. Response dated 7/01/08 to be reviewed
				Last reviewed (7/31/2006) by Dr. Art Shaw for a Nasal Spray. Adequate.
				Last reviewed (5/28/2008) by Dr. Alan Schroeder. IR sent. Response pending.
				Last reviewed (6/25/2008) by Dr. Alan Schroeder. Adequate for Inhaler mouthpiece.

(b) (4)	Last reviewed (7/25/2008) by Dr. Alan Schroeder. Adequate for Inhaler mouthpiece
	Last reviewed (5/23/2008) by Dr. Alan Schroeder. Adequate
	Last reviewed (5/27/2008) by Dr. Alan Schroeder. Adequate
	Needs review

Table 18 List of Respimat® components, materials and their function / description

No.	Component	Material	Material DMF	Function / description
(b) (4)				

No.	Component	Material	Material DMF	Function / description
(b) (4)				

CHEMISTRY NDA FILEABILITY CHECKLIST

IS THE CMC SECTION OF APPLICATION FILEABLE? Yes

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	X		
2	Is the section indexed and paginated adequately?	X		
3	On its face, is the section legible?	X		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	X		
5	Is a statement provided that all facilities are ready for GMP inspection?	X		
6	Has an environmental assessment report or categorical exclusion been provided?	X		
7	Does the section contain controls for the drug substance?	X		Reference to DMFs and NDA
8	Does the section contain controls for the drug product?	X		
9	Have stability data and analysis been provided to support the requested expiration date?	X		
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		
11	Have draft container labels been provided?	X		
12	Has the draft package insert been provided?	X		
13	Has an investigational formulations section been provided?	X		
14	Is there a Methods Validation package?	X		
15	Is a separate microbiological section included?	X		

Draft CMC Comments for the Applicant

1. As requested in the End of Phase two meeting Jan. 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.

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

/s/

Prasad Peri
11/12/2008 11:24:24 AM
CHEMIST
Acceptable for filing from CMC

Ali Al-Hakim
11/12/2008 02:10:39 PM
CHEMIST

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 21747/000	**Sponsor:**	BOEHRINGER PHARMS
Org. de:	570		900 RIDGEBURY RD
Priority:	3		RIDGEFIELD, CT 06877
Stamp Date:	08-OCT-2008	**Brand Name:**	COMBIVENT RESPIMAT
PDUFA Date:	08-AUG-2009	**Estab. Name:**	
Action Goal:		**Generic Name:**	ALBUTEROL SULFATE/ IPRATROPIUM BROMIDE
District Goal:	09-JUN-2009	**Product Number; Dosage Form: Ingredient; Potency**	
		001; SPRAY; IPRATROPIUM BROMIDE (b) (4)	
		001; SPRAY; ALBUTEROL (b) (4)	

FDA Contacts:	S. NABAVIAN	Project Manager	(HFD-570)	301-796-2777
	P. PERI	Review Chemist	(HFD-820)	301-796-1730
	A. AL HAKIM	Team Leader		301-796-1323

Overall Recommendation: ACCEPTABLE on 06-AUG-2009 by E. JOHNSON (HFD-320) 301-796-3334

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

BOEHRINGER INGELHEIM PHARMA KG
D-55216 IINGELHEIM AM RHEIN

INGELHEIM, , GERMANY

DMF No: (b) (4) **AADA:**

(b) (4)

Responsibilities:
- DRUG SUBSTANCE LABELER
- DRUG SUBSTANCE MANUFACTURER
- DRUG SUBSTANCE PACKAGER
- DRUG SUBSTANCE RELEASE TESTER
- DRUG SUBSTANCE STABILITY TESTER
- FINISHED DOSAGE LABELER
- FINISHED DOSAGE MANUFACTURER
- FINISHED DOSAGE PACKAGER
- FINISHED DOSAGE RELEASE TESTER
- FINISHED DOSAGE STABILITY TESTER

Profile: AEROSOL DISPERSED MEDICATION **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 16-NOV-2008

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Profile: (b) (4) **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 22-OCT-2008

Decision: ACCEPTABLE

[illegible]on: BASED ON PROFILE

Reference ID: 3034508

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE OTHER TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 11-JUN-2009

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE OTHER TESTER

FINISHED DOSAGE OTHER TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 06-AUG-2009

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: **CFN:** **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 10-JUN-2009

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Reference ID: 3034508

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 21747/000	**Sponsor:**	BOEHRINGER PHARMS
Org. Code:	570		900 RIDGEBURY RD
Pr /:	3		RIDGEFIELD, CT 06877
Stamp Date:	08-OCT-2008	**Brand Name:**	COMBIVENT RESPIMAT
PDUFA Date:	08-OCT-2011	**Estab. Name:**	
Action Goal:		**Generic Name:**	ALBUTEROL SULFATE/ IPRATROPIUM BROMIDE
District Goal:	09-AUG-2011	**Product Number; Dosage Form; Ingredient; Strengths**	
		001; SPRAY; IPRATROPIUM BROMIDE; (b) (4)	
		001; SPRAY; ALBUTEROL; (b) (4)	

FDA Contacts:	S. PATWARDHAN	Project Manager	(HF-01)	301-796-4085
	E. JAO	Review Chemist		301-796-1684
	A. SCHROEDER	Team Leader		301-796-1749

Overall Recommendation:	ACCEPTABLE	on 09-SEP-2011	by E. JOHNSON	(HFD-320)	301-796-3334
	WITHHOLD	on 22-AUG-2011	by EES_PROD		
	ACCEPTABLE	on 27-JUN-2011	by EES_PROD		
	PENDING	on 02-MAY-2011	by EES_PROD		
	ACCEPTABLE	on 06-AUG-2009	by EES_PROD		

Reference ID: 3034508

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG
BINGER STREET 173

INGELHEIM AM RHEIN, , GERMANY

DMF No: (b) (4) **AADA:**

(b) (4)

Responsibilities: DRUG SUBSTANCE LABELER

DRUG SUBSTANCE MANUFACTURER

DRUG SUBSTANCE PACKAGER

DRUG SUBSTANCE RELEASE TESTER

DRUG SUBSTANCE STABILITY TESTER

FINISHED DOSAGE LABELER

FINISHED DOSAGE MANUFACTURER

FINISHED DOSAGE PACKAGER

FINISHED DOSAGE RELEASE TESTER

FINISHED DOSAGE STABILITY TESTER

Profile: AEROSOL DISPERSED MEDICATION **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 20-MAY-2011

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

P : (b) (4) **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 03-MAY-2011

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE OTHER TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 03-MAY-2011

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment:	**CFN:**	**FEI:** (b) (4)	
	(b) (4)		
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE OTHER TESTER		
	FINISHED DOSAGE STERILITY TESTER		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	09-SEP-2011		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

Reference ID: 3034508