CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206756Orig1s000

CHEMISTRY REVIEW(S)

NDA 206-756

Stiolto® Respimat® (tiotropium bromide and olodaterol) Inhalation Spray, 2.5 mcg/2.5 mcg per spray*

*Expressed as tiotropium and olodaterol. Formulated with tiotropium bromide monohydrate (3.124 mcg per spray) and olodaterol hydrochloride (2.736 mcg per spray)

Boehringer Ingelheim Pharmaceuticals, Inc.

Eugenia M. Nashed, Ph.D.
Office of New Drug Quality Assessment, Division III, Branch VIII

for

Division of Pulmonary, Allergy, and Rheumatology Products

Table of Contents

Chemistry Review Data Sheet

Chemistry Review Sheet

1. NDA 206-756

2. REVIEW NUMBER: 1

3. REVIEW DATE: January 16, 2015

4. REVIEWER: Eugenia M. Nashed, Ph.D.

5. PREVIOUS DOCUMENTS: None

6. SUBMISSIONS BEING REVIEWED (Chem. Rev. #1):

Submission(s) Reviewed		Document Date
Original NDA		May 22, 2014
Amendment	(Proprietary name)	June 13, 2014
Amendment	(BC)	August 11, 2014
Amendment	(BC)	October 14, 2014
Amendment	(BC)	November 26, 2014

7. NAME AND ADDRESS OF APPLICANT:

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

8. Product Drug Code and Name:
a) Proprietary Name: Stiolto® Respimat®
b) Non-Proprietary Name (USAN): Tiotropium bromide and olodaterol inhalation spray
c) Code name/#(ONDQA only): BA 679 (tiotropium) and BI 1744 (olodaterol)
d) Chem. Type/Submission Priority (ONDQA only): S [Type 1 (NME on filing) and Type 3 (new combination)]

9. LEGAL BASIS FOR SUBMISSION: FD&C ACT 505(b)(1)
One of the APIs (olodaterol hydrochloride) was NME during NDA submission.

10. PHARMACOLOGICAL CATEGORY: LAMA/LABA Fixed Dose Combination.
Tiotropium is a long-acting anticholinergic with specificity as a muscarinic receptor antagonist (LAMA). It is approved under NDA 21-395 for Spiriva HandiHaler (Jan 30, 2004) and NDA 21-936 for Spiriva Respimat (Sep 24, 2014). Olodaterol is a long-acting beta$_2$-adrenergic agonist

(LABA). Olodaterol was considered an NME during the NDA submission; since then NDA 203108 for Striverdi Respimat (olodaterol) Inhalation Spray was approved on July 31, 2014.

11. DOSAGE FORM: Oral inhalation spray (metered)

12. STRENGTH/POTENCY:

2.5 mcg of tiotropium and 2.5 mcg of olodaterol per spray from mouthpiece (formulated with tiotropium bromide monohydrate, 3.124 mcg per spray, and olodaterol hydrochloride, 2.736 mcg per spray). Dose is two inhalation once daily (5.0 mcg of tiotropium and 5.0 mcg olodaterol).

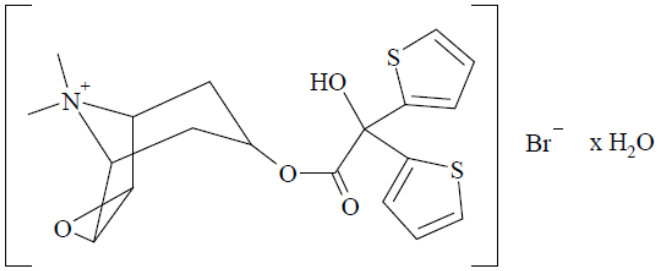
13. ROUTE OF ADMINSITRATION: Oral inhalation

14. Rx/OTC DISPENSED: __√__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:



Tiotropium bromide monohydrate

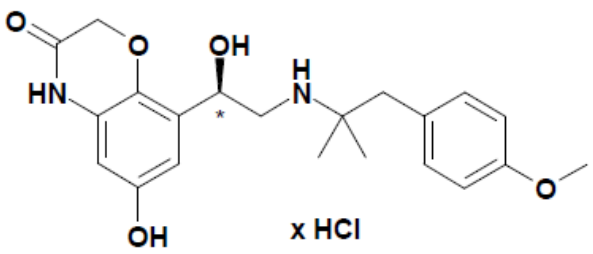
M.F. : $C_{19}H_{22}NO_4S_2Br \bullet H_2O$ M.W. : 490.4 (monohydrate); 472.4 (anhydrous)

USAN name: Tiotropium bromide

IUPAC name: (1α,2β,4β,5α,7β)-7-[(Hydroxydi-2-thienylacetyl)oxy]-9,9-dimethyl-3-oxa-9-azoniatricyclo[3.3.1.$0^{2,4}$] nonane bromide

Laboratory code: BA 679 BR

Chemistry Review Data Sheet



Olodaterol hydrochloride

Molecular formula $C_{21}H_{26}N_2O_5 \bullet HCl$ or $C_{21}H_{27}N_2O_5Cl$

Molecular mass 386.(b)(4) g/mol (free base) 422.9(b)(4) g/mol (hydrochloride)

Modified International Nonproprietary Name: Olodaterol hydrochloride

CAS Registry Number: 869477-96-3

Chemical Abstract Name: 2H-1,4-Benzoxazin-3H(4H)-one, 6-hydroxy-8-[(1R)-1-hydroxy-2-[[2-(4-methoxyphenyl)-1,1-dimethylethyl]amino]ethyl]-, monohydrochloride

Laboratory code: BI 1744 CL

Stereochemistry : The molecular structure of olodaterol (b) (4) (b) (4)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	Type	HOLDER	ITEM REFERENCED	Code[1]	Status	DATE Review Completed	COMMENTS
21,939	2	Boehringer Ingelheim Pharma, GmbH & Co.KG	Tiotropium bromide monohydrate (b) (4)	1	(b) (4)	01-22-2015 12-19-2014 Erica Englund, Ph.D. (CMC) 10-29-2008 Alan Schroeder, Ph.D. Review includes	(b) (4)

						evaluation of the (b) (4)	(b) (4)
(b) (4)	3	(b) (4)		3	Adequate Adequate	06-17-2014 Erica Englund, Ph.D. (CMC) 02-07-2013 Jessica Cole, Ph.D. (Microbiology)	LOA 06-04-2012
	3			3	Adequate	06-17-2014 Erica Englund, Ph.D.	LOA 06-04-2012

[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)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION
IND	(b) (4)	Boehringer Ingelheim Pharmaceuticals, Inc.	(b) (4)
IND	65,127	Boehringer Ingelheim Pharmaceuticals, Inc.	Tiotropium bromide Respimat® inhalation spray
IND	76,397	Boehringer Ingelheim Pharmaceuticals, Inc.	Tiotropium bromide & olodaterol Respimat® inhalation spray
NDA	21-395	Boehringer Ingelheim Pharmaceuticals, Inc.	SPIRIVA HandiHaler (tiotropium bromide) inhalation powder; original NDA (dated Dec 12, 2001; Approved Jan 30, 2004) and supplements.
NDA	203-108	Boehringer Ingelheim Pharmaceuticals, Inc.	STRIVERDI Respimat (olodaterol) inhalation spray; original NDA (dated May 14, 2012) and amendments. Approved on July 31, 2014.

Chemistry Review Data Sheet

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics	N/A			
EES (CDER OC)	Status of manufacturing and testing facilities	6/2/2014	Pending	BI site associated with the manufacturing of Respimat device is undergoing cGMP inspection in January 2014.
Pharm/Tox	Safety evaluation of controls for impurities, leachables and excipients	5/28/2014	Pending Andrew Goodwin, Ph.D.	No safety issues were identified in NonClinical Filing Rev dated 5/22/2014.
CDRH OC	Status of device manufacturing site	6/2/2014	Pending Verna/Vicenty, Ph.D.	IR comments forwarded to the Applicant (Oct 29, 2014). Applicant's response and results of the inspection at the BI site involved in Respimat manufacturing are being evaluated by the CDRH OC team.
Microbiology	Preservative effectiveness and microbial safety controls during manufacturing and release/stability testing	5/28/2014	Acceptable for Approval as of Dec 3, 2014 Jessica Cole, Ph.D.	Review covers original application and two NDA amendments (Aug 4, and Oct 2, 2014) submitted in response to IR letters.
EA	Evaluation of request for Categorical Exclusion	N/A	Acceptable	
Method Validation	N/A			Consult not planned. Drug substance and drug product methods are the same or similar to the analytical methods reviewed under NDAs for Spiriva Respimat and Striverdi Respimat.
Consults regarding drug product name, and labeling were forwarded by DPRP. Reviews by Lissa Owens (8/29/14; Proprietary name), Nichelle Rashid (9/2/14; Proprietary name granted) and Lissa Owens (9/3/14; Labeling review) are filed in DARRTS.				

The Chemistry Review for NDA 206-756

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is recommended for APPROVAL from the CMC perspective providing that an acceptable recommendation is available from the Office of Compliance (OC). The EER for the manufacturing and testing facilities is pending with the ongoing inspection at the facilities involved in the manufacturing of the Respimat device (refer to the EER Summary Report dated Jan 23, 2015, reproduced on page 58 of this review). The status for all drug master files (DMFs) supporting this application is Adequate (refer to a summary DMF table on page 6 of this review).

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

None

II. Summary of Chemistry Assessment

A. Description of Drug Substance and Drug Product:

Stiolto® Respimat® (tiotropium bromide and olodaterol) Inhalation Spray is a drug-device combination product consisting of a plastic/aluminum cartridge containing sterile aqueous formulation of tiotropium bromide and olodaterol hydrochloride, and a Respimat delivery device, which was developed by Boehringer Ingelheim (BI). Stiolto Respimat is proposed for treatment of chronic obstructive pulmonary disease (COPD).

The drug substance tiotropium bromide is approved for treatment of COPD as API in dry powder inhaler Spiriva HandiHaler (NDA 21-395; 2004), and in a liquid formulation as Spiriva Respimat (tiotropium bromide) Inhalation Spray (NDA 21-936; 2014). The drug substance olodaterol hydrochloride is approved for treatment of COPD as API in a liquid formulation of Striverdi Respimat (olodaterol) Inhalation Spray (NDA 203-108, 2014). The Respimat device is approved as an integral part of three inhalation products for treatment of COPD: Combivent Respimat (ipratropium bromide/albuterol) Inhalation Spray (NDA 21-747; 2011), Spiriva Respimat (tiotropium bromide) Inhalation Spray (NDA 21-936; 2014), and Striverdi Respimat (olodaterol) Inhalation Spray (NDA 203-108, 2014).

The drug product is manufactured by Boehringer Ingelheim in Germany and supplied as co-packaged set of cartridge and Respimat inhaler, with color coded (light green) cartridge label and device cap.

The drug product formulation is aqueous based, sterile and contained in a sealed cartridge. It contains (b) (4)% of tiotropium ((b) (4)% as tiotropium bromide monohydrate), (b) (4)% of benzalkonium chloride (b) (4), (b) (4)% of olodaterol ((b) (4)% as olodaterol hydrochloride), (b) (4)% of edetate sodium (b) (4) and hydrochloric acid (b) (4) The Applicant claims full solubility of both APIs in the drug product formulation.

The Respimat inhaler produces an aerosol by mechanical means; there are no propellant or electronic parts present. Prior to first use, the patient inserts the cartridge into the inhaler and a piercing of the sterile cartridge occurs during this time. After priming (visible mist + 3 sprays) each actuation delivers from mouthpiece 2.5 mcg of tiotropium (corresponding to 3.124 mcg of titropium bromide monohydrate, which is used in formulation) and 2.5 mcg of olodaterol (corresponding to 2.736 mcg of olodaterol hydrochloride which is used in formulation) in (b) (4) µL spray volume. A dose is comprised of two actuations, i.e., 5.0 mcg of tiotropium and 5.0 mcg of olodaterol delivered in (b) (4) µL volume, with metered volume of (b) (4) µL (b) (4) The Respimat device contains an actuation counter. The commercial device delivers 60 actuations (30 doses) after priming and it locks to prevent further use. Also, there is a physician sample version which delivers 28 actuations (14 doses) after priming.

The drug substance, tiotropium bromide monohydrate is a white (b) (4) crystalline powder which is slightly soluble in water (b) (4) and methanol (b) (4) It is practically insoluble in methylene chloride. (b) (4)

Tiotropium bromide is a quaternary ammonium salt (b) (4) It is a long-acting anticholinergic with specificity for muscarinic receptor antagonist (LAMA). The manufacturing and quality of the drug substance is controlled under DMF (b) (4) The same quality tiotropium bromide monohydrate is present in two approved drug products: Spiriva HandiHaler (tiotropium bromide) Inhalation Powder, NDA 21-395 (Approved Jan 30, 2004) and Spiriva Respimat (tiotropium bromide) Inhalation Spray, NDA 21-936 (Approved Sep 24, 2014).

The drug substance, olodaterol hydrochloride is a white crystalline solid (b) (4) well soluble (b) (4) in water (b) (4) (b) (4) The molecule is (b) (4) (b) (4) (BI code: BI 1744 CL). The drug substance is a long-acting beta2-adrenergic agonist (LABA). The synthesis and controls for olodaterol hydrochloride were reviewed under NDA 203-108 (Striverdi Respimat (olodaterol) Inhalation Spray and were found adequate to support the inhalation spray product (Dr. Craig Bertha, 7/30/2012). The above NDA is cross-referenced to this NDA.

Olodaterol drug substance was considered NME during the NDA submission; since then NDA 203-108 for Striverdi Respimat (olodaterol) Inhalation Spray was approved on July 31, 2014.

Note:
Two strengths for Stiolto Respimat (tiotropium bromide / olodaterol) Inhalation Spray (1.25 µg / 2.5 µg and 2.5 µg / 2.5 µg per actuation) were developed and used in Phase 3 clinical trials. The Applicant provided CMC documentation describing both strengths (Module 3), however only the 2.5 µg /2.5 µg product is proposed for marketing. The CMC data pertaining to the 1.25 µg/2.5 µg strength were reviewed and are considered adequate to support the comparability of the *in vitro* dose performance for the two strengths (including the *in vitro* dose proportionality) for the purpose of use in clinical program. The 1.25 µg /2.5 µg combination product was not fully reviewed for the purpose of marketing.

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

Stiolto® Respimat® (tiotropium bromide and olodaterol) Inhalation Spray is a multidose drug-device combination product for the long-term maintenance treatment of patient with COPD. A once-daily treatment comprises of two inhalations from the mouthpiece of Respimat inhaler for a total of 5 mcg of tiotropium and 5 mcg of olodaterol.
To use the drug product, the patient needs to remove the clear base of the inhaler and insert the matching cartridge and replace the clear base. With the device in the upright position the clear base is turned right (directing arrows on the label) until click is heard, and after opening the light green-colored cap the trigger button is released actuating the device. The inhaler has to be primed until fine mist is visible and then actuated additional 3 times. To obtain a dose patient needs to exhale, seal the lips around the mouthpiece of the inhaler and actuate the device while inhaling slowly and deeply. A single re-priming actuation is needed if the device is not used for more than 3 and up to 21 days. After non-use for more than 21 days the initial priming procedure needs to be repeated.

The drug product should be stored at 25^{o}C (77^{o}F); excursions permitted to 15^{o}C to 30^{o}C (59^{o}F to 86^{o}F) [see USP Controlled Room Temperature]. Freezing conditions should be avoided. The proposed expiry period of 36 months is supported by 36 months of real time stability data submitted for 3 batches of the commercial drug product.
The in use expiry (after the cartridge is inserted into inhaler) is 3 months, and it is supported by in-use stability data.

C. Basis for Approvability Recommendation

The application is recommended for approval providing acceptable recommendation from the Office of Compliance (OC), and the CDRH OC review teams evaluating the application.

D. Summary of Quality Assessment

The overall quality assessment based on the evaluation of Critical Quality Attributes (CQA) is summarized in table below.

DP attribute/ CQA	Factors that can impact the CQA[1]	O[2]	S[4, 3]	D[4]	FMECA RPN #	Comments & Considerations
Spray Content Uniformity (SCU)	• Low formulation assay of either API • Lower than target fill of cartridge • Failure of protective packaging for the formulation (aluminum cylinder) • Device malfunction • Integrity of cartridges (leakage) • Interaction of APIs	2	2	2	**8**	(b) (4) • Final drug product specification includes tests for both formulation assays and SCU (b) (4) • See referenced DMF (b) (4) for Respimat device manufacture and control and note that device is already approved for applicant's drug products of N21747 (Combivent Respimat), N21936 (Spiriva Respimat) and N203108 (Striverdi Respimat); cartridge dimensions (important for function) have IPC (b) (4) • SCU data appear to be reasonably comparable to that obtained from monotherapy drug products (see P.2.; requested at pre-NDA meeting)
Aerodynamic Particle Size Distribution (APSD)	• Low assay of either API in formulation • Viscosity/surface tension change • Lower than target fill of cartridge • Failure of protective packaging for the formulation • Device malfunction (b) (4) • Laser diffraction (LD) testing used as surrogate for more typical cascade impactor (CI) measurements	2	2	2	**8**	(b) (4) • (b) (4); see referenced DMF (b) (4) also note device already approved for applicant's drug product of N21747, N21936 and N203108 (b) (4) • Applicant provides data in the justification of specifications section to support use of LD as an alternative versus CI measurements for APSD • APSD data appear reasonably comparable to that obtained from monotherapy drug products (see P.2.; Agency requested these data at the pre-NDA meeting)
Purity (impurities/ degradants)	• Degradation of APIs as formulated • Input purity of APIs • Input purity of other formulation components • Leaching from CCS components into formulation • pH of formulation • Integrity of cartridges • Interaction of APIs	1	2	2	**4**	• Compatibility of APIs and excipients already established in earlier NDAs for the monotherapy products. • CCS components already observed to be compatible with monotherapy formulations The applicant has an (b) (4) for the formulation pH (b) (4) • Stability data can be examined to assess potential for chemical interaction between APIs
Microbial quality	• To be addressed by the microbiology team in OPS					

[1] Based on underlying assumption that patients use the device as intended (human factors beyond scope of CMC evaluation).

[2] O = Probability of Occurrence; S = Severity of Effect; D = Detectability

[3] Severity of effect can only be estimated; input from clinical or pharmacology/toxicology team would be necessary for more accurate assessment of clinical impact of failures of product CQAs.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block
Chemistry Reviewer: Eugenia Nashed, Ph.D.
Acting CMC Lead: Craig Bertha, Ph.D.
Acting Branch Chief: Julia Pinto, Ph.D.

Office of New Drug Quality Assessment (ONDQA), Division III

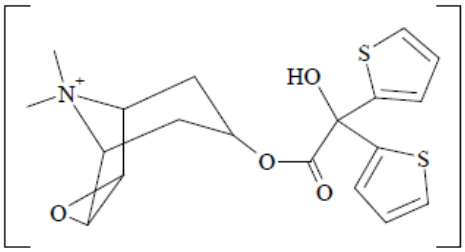
CHEMISTRY ASSESSMENT

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data

S. DRUG SUBSTANCE [Tiotropium Bromide Monohydrate and Olodaterol Hydrochloride]

S.1 General Information
S.1.1 Nomenclature
S.1.2. Structure
S.1.3 General Properties

Tiotropium Bromide Monohydrate



M.F. : $C_{19}H_{22}NO_4S_2Br \cdot H_2O$ M.W. : 490.4 (monohydrate); 472.4 (anhydrous)

USAN name: Tiotropium bromide

IUPAC name: (1α,2β,4β,5α,7β)-7-[(Hydroxydi-2-thienylacetyl)oxy]-9,9-dimethyl-3-oxa-9-azoniatricyclo[3.3.1.$0^{2,4}$] nonane bromide

Laboratory code: BA 679 BR

Tiotropium bromide is a quaternary ammonium salt (b) (4)
Tiotropium bromide monohydrate is a white hygroscopic crystalline powder which is slightly soluble in water (b) (4) and methanol (b) (4) It is practically insoluble in methylene chloride. (b) (4)

Tiotropium bromide monohydrate is an API in the approved drug product: Spiriva HandiHaler (tiotropium bromide) Inhalation Powder, NDA 21-395 (Approved 2004) and Spiriva Respimat (tiotropium bromide) Inhalation Spray, NDA 21-936 (Approved 2014).

S.2 Manufacture
S.2.1 Manufacturers
S.2.2 *Manufacturing Process and Controls*
The manufacturer of tiotropium bromide monohydrate is Boehringer Ingelheim Pharma GmbH & Co. KG, 55216 Ingelheim am Rhein, Germany. The active ingredient is (b) (4)

36 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

EVALUATION

The support data for the container closure are adequate. Both, the cartridge and the Respimat inhaler are supported by DMFs ((b) (4) for cartridge and (b) (4) for inhaler) held by the Applicant. Both DMFs have adequate status (refer to DMF table on page 6 of this review). The Respimat device is approved as an integral part of three inhalation products for treatment of COPD: Combivent Respimat (ipratropium bromide/albuterol) Inhalation Spray (NDA 21-747; 2011), Spiriva Respimat (tiotropium bromide) Inhalation Spray (NDA 21-936; 2014), and Striverdi Respimat (olodaterol) Inhalation Spray (NDA 203-108, 2014). (b) (4) The performance of the device with the Stiolto combination formulation seems very similar to the performance with Spiriva and Striverdi formulations.

The review of the facilities involved in the manufacturing and testing of the Respimat device is currently pending with the Office of Compliance (OC). The CDRH OC team requested additional data from the Applicant (IR dated Oct 29, 2014) regarding submission of the procedures and information required under 21 CFR 820.20, 820.30, 820.50, 820.80 and 820.100. The Applicant provided comprehensive response on November 26, 2014, which based on the preliminary discussion with the quality review team seems adequate. Detailed evaluation of the response, together with the evaluation of the results of pending inspection at the device-related establishment will be filled in the consult review by Drs. Verna and Vicenty from the CDRH OC.

P.8 Stability [Stiolto Respimat Inhalation Spray]

The Applicant is requesting a shelf-life of 36 months for this combination product when stored at 25°C (77°F) with excursions permitted to 15 - 30°C (59 - 86°F) [see USP Controlled Room Temperature]. After the cartridge is inserted into the Respimat inhaler, 3 months of in-use expiry period is requested for product stored at the controlled room temperature (do not freeze). Refer to summary table reproduced below. The same expiry period is requested for both drug product presentations, 60 sprays and 28 sprays.

Table 2 Preliminary stability and packaging information

Container Closure System	Recommended Shelf-Life [months]	Recommended Storage Information
Cartridge for RESPIMAT inhaler and RESPIMAT inhaler (60 and 28 actuations)	36 months	Store at 25°C (77°F), excursions permitted to 15 - 30°C (59 - 86°F) Do not freeze In-use shelf-life: 3 months Discard 3 months after insertion of cartridge into inhaler

In support, stability data for three primary stability batches (2.5 mcg/2.5 mcg) tested at 25°C /60%RH (shelf-life) for 36 months and at 40°C /75%RH (accelerated conditions) for 6 months are submitted. The batches were manufactured at the commercial facilities, using commercial process and packaged in the commercial container system. In addition, supportive data for three clinical batches of the 1.25 mcg/2.5 mcg strength of the combination product, stored for 18-24 months at 25°C /60%RH (shelf-life) and 6 months at 40°C /75%RH (accelerated conditions), are submitted.

Batch number of RESPIMAT cartridge/ inhaler batch	Batch size	RESPIMAT inhaler	Date of cartridge manufacture	Available stability data
903282- 8L0014	(b) (4)	Respimat (60 actuations)	March, 2009	36 months
903283-8L0023		Respimat (60 actuations)	April, 2009	36 months
903284-8L0009		Respimat (60 actuations)	April, 2009	36 months

Stability of the APIs in the Combination Formulation (3 primary stability batches)

Tiotropium API Stability

(b) (4)

Olodaterol API Stability

(b) (4)

Stability results obtained for a typical batch of 2.5 mcg/2.5 mcg drug product are reproduced below for a reference.

5 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page.

A APPENDICES

A.1 Facilities and Equipment

Overall OC Recommendation:

The overall recommendation for this NDA is Pending as of Jan 22, 2015, the completion date of this review. Refer to the copy of the EES Summary Report dated Jan 22, 2015, and reproduced below for a reference.

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application:	NDA 206756/000	**Action Goal:**	
Stamp Date:	22-MAY-2014	**District Goal:**	22-DEC-2014
Regulatory:	22-MAY-2015		
Applicant:	BOEHRINGER PHARMS	**Brand Name:**	TIOTROPIUM / OLODATEROL RESPIMAT
	900 RIDGEBURY RD	**Estab. Name:**	
	RIDGEFIELD, CT 06877	**Generic Name:**	TIOTROPIUM / OLODATEROL RESPIMAT
Priority:	14	**Product Number; Dosage Form; Ingredient; Strengths**	
Org. Code:	570	001; SPRAY; TIOTROPIUM BROMIDE; 2.5MCG 001; SPRAY; OLODATEROL HYDROCHLORIDE; 2.5MCG	

Application Comment:

FDA Contacts:	E. NASHED	Prod Qual Reviewer	(HFD-820)	3017961723
	Y. LIU	Product Quality PM		3017961926
	C. FORD	Regulatory Project Mgr	(HFD-570)	3017963420
	C. BERTHA	Team Leader		3017961646

Overall Recommendation: PENDING on 19-JUN-2014 by EES_PROD

Chemistry Assessment Section

Establishment: **CFN:** 9610492 **FEI:** 3002806556

BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG

BINGER STREET 173
INGELHEIM AM RHEIN, RHEINLAND-PFALZ, GERMANY

DMF No: **AADA:**

Responsibilities:
DRUG SUBSTANCE MANUFACTURER
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

Establishment Comment: KLAUS.HELLER@BOEHRINGER-INGELHEIM.COM (on 18-JUN-2014 by Y. LIU () 3017961926)

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

NON-STERILE API BY CHEMICAL SYNTHESIS NONE

DEVICE KIT ASSEMBLER NONE

SUBMITTED TO OC	19-JUN-2014			LIUY
SUBMITTED TO DO PDUFA: 22-NOV-2014 NME	25-JUN-2014	Product Specific and GMP Inspection		DOBBINE
ASSIGNED INSPECTION TO IB	27-JUN-2014	Product Specific and GMP Inspection		TUNGL
DO RECOMMENDATION	30-JUN-2014		ACCEPTABLE	MROSE
OC RECOMMENDATION	30-JUN-2014		ACCEPTABLE	SHARPT
SUBMITTED TO OC	19-JUN-2014			LIUY
SUBMITTED TO DO PDUFA: 22-NOV-2014	24-JUN-2014	Product Specific and GMP Inspection		DOBBINE

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

(b) (4)

DMF No: **AADA:**

Responsibilities:
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Establishment Comment: DRUG PRODUCT: ANALYTICAL TESTING (ALL RELEASE & STABILITY TESTS EXCEPT STERILITY) (on (b) (4) by Y. LIU () 3017961926)

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

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					
SUBMITTED TO OC	(b) (4)				LIUY
OC RECOMMENDATION	24-JUN-2014			ACCEPTABLE	DOBBINE

Chemistry Assessment Section

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

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE STERILITY TESTER

Establishment Comment:

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

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					
SUBMITTED TO OC	(b) (4)				LIUY
OC RECOMMENDATION	24-JUN-2014			ACCEPTABLE	DOBBINE

Establishment: **CFN:** 9610492 **FEI:** 3002806556
BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG
BINGER STREET 173
INGELHEIM AM RHEIN, RHEINLAND-PFALZ, GERMANY
DMF No: 18135 **AADA:**
Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE OTHER TESTER
DRUG SUBSTANCE PACKAGER
DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER
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: 10-JUN-2014
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION
Profile: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE
Last Milestone: DO RECOMMENDATION
Milestone Date: 11-APR-2014
Decision: WITHHOLD
Reason: REGULATORY ACTION TAKEN AND/OR PREVIOUS DEVIATIONS PERSIST WITH PRODUCT SPECIFIC ISSUES

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)
(b) (4)
DMF No: **AADA:**
Responsibilities: FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER
Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 15-APR-2014
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment:	**CFN:** (b) (4)	**FEI:** (b) (4)	
	(b) (4)		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE STERILITY TESTER		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	04-APR-2014		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

Establishment:	**CFN:**	**FEI:** (b) (4)	
	(b) (4)		
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE RELEASE TESTER FINISHED DOSAGE STERILITY TESTER		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	18-APR-2014		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Establishment:	**CFN:**	**FEI:** (b) (4)	
	(b) (4)		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE LABELER FINISHED DOSAGE PACKAGER		
Profile:	AEROSOL DISPERSED MEDICATION	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	22-JUL-2014		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Establishment:	**CFN:** (b) (4)	**FEI:** (b) (4)	
	(b) (4)		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE LABELER FINISHED DOSAGE PACKAGER		
Profile:	AEROSOL DISPERSED MEDICATION	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	15-MAY-2014		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Chemistry Assessment Section

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

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE OTHER TESTER

FINISHED DOSAGE STERILITY TESTER

Establishment Comment: TIOTROPIUM DRUG SUBSTANCE: MICROBIOLOGICAL TESTING. (b) (4)

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

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					
SUBMITTED TO OC	19-JUN-2014				LIUY
SUBMITTED TO DO	24-JUN-2014	Product Specific and GMP Inspection			DOBBINE
PDUFA: 22-NOV-2014					
ASSIGNED INSPECTION TO IB	27-JUN-2014	Product Specific and GMP Inspection			TUNGL
ASSIGNED INSPECTION TO IB	27-JUN-2014	Product Specific and GMP Inspection			TUNGL
INSPECTION SCHEDULED	(b) (4)				KSEGO

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

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE LABELER

Establishment Comment:

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

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					
SUBMITTED TO OC	(b) (4)				LIUY
SUBMITTED TO DO	24-JUN-2014	10-Day Letter			DOBBINE
DARRTS SHOWS AN INSPECTION,HOWEVER, NO PROFILES WERE ENTERED.					
DO RECOMMENDATION	22-JUL-2014			ACCEPTABLE	KCULVER
GMP EI ENDING 7/9/14 WAS VAI.					
OC RECOMMENDATION	22-JUL-2014			ACCEPTABLE	SAFAAIJAZIR

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

(b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE LABELER

Establishment Comment:

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

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					
SUBMITTED TO OC	(b) (4)				LIUY
SUBMITTED TO DO	24-JUN-2014	Product Specific and GMP Inspection			DOBBINE
PDUFA: 22-NOV-2014					
ASSIGNED INSPECTION TO IB	(b) (4)	GMP Inspection			DOMBROWSKIR
SECONDARY PACKAGING ONLY - UPDATE PROFILE					

A.2 Adventitious Agents Safety Evaluation

Not applicable. Microbial safety review is pending.

A.3 Novel Excipients

Not applicable; no novel excipients are used in the formulation.

R REGIONAL INFORMATION

R1 Executed Batch Records

The English translations of Batch Records are provided in section 3.2.R and noted. The updated sterilization processes and controls for microbial safety are under review by the Microbiology Review team.

R2 Comparability Protocols

No Comparability Protocol is requested in this submission.

R3 Methods Validation Package

Method Validation Package is submitted. A revalidation request is not planned since only compendial methods or standard HPLC methods are used in this application. Also, the drug substance and drug product analytical methods are (b) (4)

II. Review of Common Technical Document-Quality (Ctd-Q) Module 1

A. Labeling & Package Insert

The comments on the CMC portion of the label is provided directly on the working copy of the package insert during team meetings.

Name and Description:

(b) (4)

How Supplied:

STIOLTO RESPIMAT Inhalation Spray is supplied in a carton containing one STIOLTO RESPIMAT cartridge and one STIOLTO RESPIMAT inhaler.

The STIOLTO RESPIMAT cartridge is provided as an aluminum cylinder with a tamper protection seal on the cap. The STIOLTO RESPIMAT cartridge is only intended for use with the STIOLTO RESPIMAT inhaler.

The STIOLTO RESPIMAT inhaler is a cylindrical shaped plastic inhalation device with a gray colored body and a clear base. The clear base is removed to insert the cartridge. The inhaler contains a dose indicator. The light green colored cap (b) (4) The written information on the label of the gray inhaler body indicate that it is labeled for use with the STIOLTO RESPIMAT cartridge (b) (4).

STIOLTO RESPIMAT Inhalation Spray: 60 metered actuations (NDC 0597-0155-61)
STIOLTO RESPIMAT Inhalation Spray: 28 metered actuations (NDC 0597-0155-31)
(b) (4))

Rx Only
Distributed by:
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, CT 06877 USA

Storage:

Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Avoid freezing.

The copies of provided container and carton labels are provided below for a reference.

(b) (4)

(b) (4)

[redacted]

B. Environmental Assessment or Claim of Categorical Exclusion

The Applicant applied for categorical exclusion under 21 CFR 25.31(b), for both active ingredients, as follow.

> Estimation of the concentration of the substance at the point of entry into the aquatic environment was calculated based on the July 1998 Guidance for Industry: Environmental Assessment of Human Drug and Biologics Applications using the equation:
>
> EIC-Aquatic (ppb) = A x B x C x D where
> A = kg/year produced for direct use (as active moiety)
> B = 1/liters per day entering POTWs*
> C = year/365 days
> D = 10^9 µg/kg (conversion factor)
> * (b) (4) liters per day entering publicly owned treatment works (POTWs),
>
> The estimated concentration is based on the maximum expected annual direct usage during the peak year within the first five years in the marketplace after approval of this request (Confidential Appendix 1). This results in an estimated concentration of each substance at the point of entry into the aquatic environment below 1 ppb due to this action (Confidential Appendix 2). Estimated concentrations are based on usage of this product, and all other products either approved or pending approval, containing these active moieties.

EVALUATION
Acceptable. These were evaluated and considered adequate during the reviews for NDA 21-936 (Spiriva Respimat, 2014) and NDA 203-108 (Striverdi Respimat, 2014).

Initial Manufacturing (CGMP/Facilities) Assessment (IMA) and Filing Review for Pre-Marketing Applications (Original)

I. Review Cover Sheet

1. OMPQ Reviewer: Linda Ng, Ph.D.

2. NDA/BLA Number: NDA 206756
   Submission Date: May 22, 2014
   21st C. Review Goal Date: September 22, 2014
   PDUFA Goal Date: November 22, 2014

3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	Stiolto™ Respimat®
Established or Non-Proprietary Name (USAN) and strength:	Tiotropium/Olodaterol Inhalation Spray
Dosage Form:	Sterile inhalation spray

4. SUBMISSION PROPERTIES:

Review Priority :	PRIORITY
Applicant Name:	Boehringer Ingelheim
Responsible Organization (OND Division):	DPARP

II. Application Detail

1. INDICATION: For long-term, once-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

1. ROUTE OF ADMINISTRATION: Oral inhalation

2. STRENGTH/POTENCY: (b) (4) 2.5 mcg tiotropium/2.5 mcg olodaterol per actuation

3. Rx/OTC DISPENSED: X ☐Rx ☐OTC

4. ELECTRONIC SUBMISSION (yes/no)? Yes

5. PRIORITY CONSIDERATIONS:

	Parameter	Yes	No	Unk	Comment
1.	NME / PDUFA V		X		
2.	Breakthrough Therapy Designation		X		
3.	Orphan Drug Designation		X		
4.	Unapproved New Drug		X		
5.	Medically Necessary Determination		X		
6.	Potential Shortage Issues [either alleviating or non-approval may cause a shortage]		X		
7.	Rolling Submission		X		
8.	Drug/device combination product with consult	X			The inhalation spray product uses the Respimat device, which we have already approved as part of the Combivent drug product (Spiriva and Striverdi Respimats are still under review
9.	Complex manufacturing		X		
10.	Other (e.g., expedited for an unlisted reason)		X		

III. FILING CHECKLIST

The following parameters are necessary in order to initiate a full review (i.e., the application is complete enough to start review but may have deficiencies). On **initial** review of the NDA application:

A. COMPLETENESS OF FACILITY INFORMATION				
	Parameter	**Yes**	**No**	**Comment**
11.	Is all site information complete (e.g., contact information, responsibilities, address)?	X		
12.	Do all sites indicate they are ready to be inspected (on 356h)?	X		
13.	Is a single comprehensive list of all involved facilities available in one location in the application?	X		
14.	For testing labs, is complete information provided regarding which specific test is performed at each facility and what stage of manufacturing?	X		
15.	Additional notes (non-filing issue) 1. Are all sites registered or have FEI #? 2. Do comments in EES indicate a request to participate on inspection(s)? 3. Is this first application by the applicant?	X		
			X	
			X	

*If any information regarding the facilities is missing/omitted, communicate to OPS/ONDQA regarding missing information and copy EESQuestions. Notify OMPQ management if problems are not resolved within 3 days and it can be a *potential* filing issue.

B. DRUG SUBSTANCE (DS) / DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
16.	Have any Comparability Protocols been requested?		X	

IMA CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
17.	Does this application fit one of the EES Product Specific Categories?	X		Olodaterol is considered an NME because the NDA for the monotherapy has not yet been approved
18.	Have EERs been cross referenced against the 356h and product specific profile for accuracy and completion? Have all EERs been updated with final PAI recommendation?	X		
19.	**From a CGMP/facilities perspective, is the application fileable?** If the NDA is not fileable from a product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.	X		

IV. Manufacturing Summary: Critical Issues and Complexities

Does the submission contain any of the following elements? No			
Nanotechnology	RTRT Proposal	PAT	Drug/Device Combo
☐	☐	☐	☐
PET	Design Space	Continuous Mfg	Naturally derived API
☐	☐	☐	☐
Other (explain):			

Manufacturing Highlights

1. Drug Substance

	Parameter	Yes	No	Comment
	Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, unusual control strategy)?		X	

Include process flow chart/diagram (see eCTD Section 2.3.S.1)

2. Drug Product

	Parameter	Yes	No	Comment
	Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, unusual control strategy)?		X	

Include process flow chart/diagram (see eCTD Section 2.3.P.1)

Schematic drawing of the cartridge

1.1 MANUFACTURING FLOW CHART

Environmental conditions (class)	STEPS	NAMES OF CONSTITUENTS	OPERATION	PROCESS CONTROLS	EQUIPMENT
(b) (4)					

Environmental conditions (class)	STEPS	NAMES OF CONSTITUENTS	OPERATION	PROCESS CONTROLS	EQUIPMENT

(b) (4)

3. Facility-Related Risks (e.g., expected in-process testing not being performed, questionable development, unexplained stability failures, data integrity issues, etc.).

Describe any potential 21CFR 211 compliance issues. None that is obvious

4. **Drug Product Facility Inspectional History that could impact the manufacturing of this product** All except one facility are acceptable. The facility, (b) (4) was added later due to an inclusion of device capability. The same facility has been cleared for DP manufacturing.

Additional information not covered above None

1 Page has been Withheld in Full as b4 (CCI/TS) immediately following this page.

For each EER, indicate PAI recommendation on the Manufacturing Facilities Chart above (e.g., PS, GMP, 10 Day, AC based on file review). This is the recommendation that will be entered into EES. **For PAI, include the reason for the PAI (i.e. PAI Trigger) in the comment section of the facilities chart.**

V. Overall Conclusions and Recommendations

Is the application fileable? (yes/no, Yes to questions 11-12) Yes
Based on Section IV, is a KTM warranted for any PAI? (yes/no). If yes, please identify the sites in the above chart. No KTM warranted. No inspection expected.
Are there comments/issues to be included in the 74 day letter, including appropriate identification of facilities? (yes/no) No
Comments for 74 Day Letter
1.
2.
3.

REVIEW AND APPROVAL

(DARRTS)

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

/s/

LINDA L NG
08/13/2014

MAHESH R RAMANADHAM
08/13/2014

IQA and Filing Review Cover Sheet

1. NEW DRUG APPLICATION NUMBER: N206756

2. DATES AND GOALS:

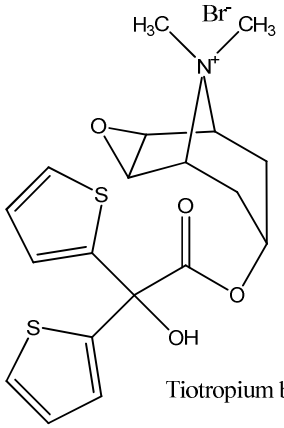
Letter Date: 22-MAY-2014	Submission Received Date : 22-MAY-2014
PDUFA Goal Date: 22-NOV-2014 (as per DARRTS)	

3. PRODUCT PROPERTIES:

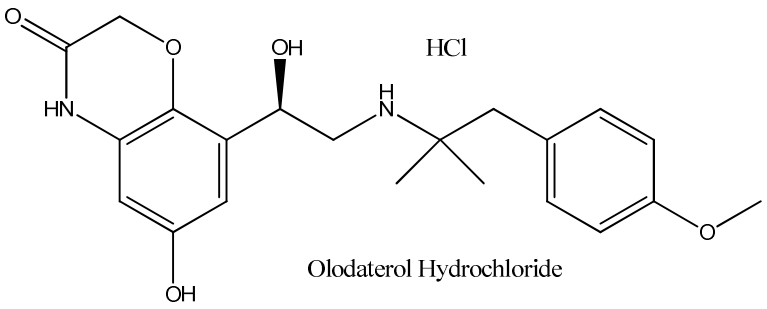
Trade or Proprietary Name:	Stiolto™ Respimat®
Established or Non-Proprietary Name (USAN):	Tiotropium and olodaterol
Dosage Form:	Inhalation spray
Route of Administration	Oral inhalation
Strength/Potency	(b) (4) 2.5 mcg tiotropium/2.5 mcg olodaterol per actuation
Rx/OTC Dispensed:	Rx X OTC

4. INDICATION: For long-term, once-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

5. DRUG SUBSTANCE STRUCTURAL FORMULAE:



Tiotropium bromide



Olodaterol Hydrochloride

6. NAME OF APPLICANT (as indicated on Form 356h): Boehringer Ingelheim Pharmaceuticals, Inc.

7. SUBMISSION PROPERTIES:

Review Priority:	Priority (as per DARRTS)
Submission Classification (Chemical Classification Code):	Based on draft MaPP 7500.3, Type 3 & 4: New Dosage Form (for tiotropium) and New Combination
Application Type:	505(b)(1)
Breakthrough Therapy	Yes No X
Responsible Organization (Clinical Division):	DPARP

8. CONSULTS:

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics			Some trends are noted in the stability data: 1) increase in tiotropium related degradants; 2) concomitant drop in tiotropium content. It is recommended that, although neither drug is an NME, the reviewer consider the principles outlined in ICH Q1E when evaluating the applicant's proposed expiration dating period and stability data.
Clinical Pharmacology		X	
Establishment Evaluation Request (EER)	X		The ONDQA PM was informed of the arrival of the application on 30-MAY-2014; The submission of the EER to Office of Compliance is pending.

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Pharmacology/Toxicology		X	It is unlikely that a consult to the pharmacology/toxicology group will be necessary based on this preliminary review.
Methods Validation			It will be left to the reviewer to decide if it is warranted to send any methods for assessment by the Agency laboratory, based on evaluation of the methods and the associated validation data provided.
Environmental Assessment			The applicant claims categorical exclusion as per 21 CFR 25.31. The reviewer can consult with the OPS EA expert (R. Bloom, PhD) if the calculations (see confidential appendix 2) related to the expected introduction concentration are determined to be questionable.
CDRH		X	It is noted that the Respimat® device is already approved for the Combivent® drug product of N20291.
Other			N/A

Overall Filing Conclusions and Recommendations

CMC:

Is the Product Quality Section of the application fileable from a CMC perspective?
Yes X No
CMC Filing Issues:
N/A

Are there potential CMC review issues to be forwarded to the Applicant with the 74-Day letter?
Yes No X
CMC Comments for 74-Day Letter (assuming filing):
1.

Biopharmaceutics:

Is the Product Quality Section of the application fileable from a Biopharmaceutics perspective?
Yes X No
Biopharmaceutics Filing Issues:
There is no biopharmaceutics information in the application. After discussion with the biopharmaceutics team leader Tapash Ghosh, PhD, it was decided that a biopharmaceutics filing review/IQA was not necessary.

Are there potential Biopharmaceutics review issues to be forwarded to the Applicant with the 74-Day letter?
Yes No X
Biopharmaceutics Comments for 74-Day Letter:
N/A

Microbiology:

Is the Product Quality Section of the application fileable from a Microbiology perspective?
Yes No
Microbiology Filing Issues:
The CDER OPS IO MICRO mailbox was sent a notification of the application.

Summary of Initial Quality Assessment

Does the submission contain any of the following elements?			
Nanotechnology	QbD Elements	PET	Other, please explain
No	No	No	N/A

Is a team review recommended?	Yes	No X
Suggested expertise for team:		

Summary of Critical Issues and Complexities: See the summary list below at the beginning of the IQA review.

N/A

DP attribute/ CQA	Factors that can impact the CQA[1]	O[2]	S[4, 3]	D[4]	FMECA RPN #	Comment & considerations
Spray Content Uniformity (SCU)	• Low formulation assay of either API • Lower than target fill of cartridge • Failure of protective packaging for the formulation (aluminum cylinder) • Device malfunction • Integrity of cartridges (leakage) • Interaction of APIs	2	2	2	8	(b) (4) • Final drug product specification includes tests for both formulation assays and SCU (b) (4) • See referenced DMF (b) (4) for Respimat device manufacture and control and note that device is already approved for applicant's drug product of N21747 (Combivent Respimat); cartridge dimensions (important for function) have IPC (b) (4) • SCU data appear to be reasonably comparable to that obtained from monotherapy drug products (see P.2.; requested at pre-NDA meeting)
Aerodynamic Particle Size Distribution (APSD)	• Low assay of either API in formulation • Viscosity/surface tension change • Lower than target fill of cartridge • Failure of protective packaging for the formulation • Device malfunction (b) (4) • Laser diffraction (LD) testing used as surrogate for more	2	2	2	8	(b) (4) • (b) (4) see referenced DMF (b) (4) (also note device already approved for applicant's drug product of N21747 (Combivent Respimat) (b) (4) • Applicant provides data in the justification of specifications

[1] Based on underlying assumption that patients use the device as intended (human factors beyond scope of CMC evaluation).
[2] O = Probability of Occurrence; S = Severity of Effect; D = Detectability
[3] Severity of effect can only be estimated; input from clinical or pharmacology/toxicology team would be necessary for more accurate assessment of clinical impact of failures of product CQAs.

	typical cascade impactor (CI) measurements					section to support use of LD as an alternative versus CI measurements for APSD • APSD data appear reasonably comparable to that obtained from monotherapy drug products (see P.2.; Agency requested these data at the pre-NDA meeting)
Purity (impurities/degradants)	• Degradation of APIs as formulated • Input purity of APIs • Input purity of other formulation components • Leaching from CCS components into formulation • pH of formulation • Integrity of cartridges • Interaction of APIs	1	2	2	4	• Compatibility of APIs and excipients already established in earlier NDAs for the monotherapy products. • CCS components already observed to be compatible with monotherapy formulations The applicant has an (b) (4) for the formulation pH (b) (4) • Stability data can be examined to assess potential for chemical interaction between APIs
Microbial quality	• To be addressed by the microbiology team in OPS					

INITIAL QUALITY ASSESSMENT

The applicant has previously submitted two applications for the monotherapy versions of this combination drug product [N203108 for the Striverdi (olodaterol) Respimat and N21936 for the Spiriva (tiotropium bromide) Respimat; neither have been approved due to inspectional issues]. They have also had the combination drug product Combivent (ipratropium bromide/albuterol sulfate) Respimat approved recently under N21747, and this drug product uses the same device as these other applications (Respimat (b) (4) Inhaler). As a result, most of the CMC-related issues are expected to have been resolved as a result of the evaluation and interaction with the applicant for the previous applications. The current drug product was developed under I76397.

Tiotropium is currently not an NME as the applicant has an approved inhalation powder drug product for COPD with this drug. However, olodaterol, a long-acting beta agonist, is still considered an NME as the applicant's application for the monotherapy olodaterol inhalation spray drug product (Striverdi Respimat, N203108) is not approved yet.

The drug product prepared with the olodaterol hydrochloride and tiotropium bromide drug substances is an inhalation spray which consists of a sterile aqueous solution of the formulation that is metered by a Respimat® inhaler providing multiple discrete doses of aerosolized formulation from a mouthpiece. There is no propellant and the Respimat® device provides mechanical energy (b) (4) to generate an aerosol of the formulation. Each actuation delivers 2.5 mcg of olodaterol (b) (4) from the mouthpiece along with (b) (4) 2.5 mcg of tiotropium (b) (4) There are two presentations of each strength, a trade presentation that delivers 60 actuations and a physician sample presentation that delivers 28 actuations. The formulation is contained in a plastic container inside an aluminum cylinder and insertion of the cartridge by patients prior to first use involves piercing of the cartridge by the device for access to the formulation. The in-use period after insertion of the cartridge is said to be 3 months. Both of these have identical fills but lock out at different points. Recall that a daily dose is two actuations once a day. The following figures from the proposed labeling show two views of the device and the cartridge.

Start of Applicant Material

End of Applicant Material

Because the device was under development by BI for so many years, and the applicant had submitted previous drug products that used this device, the CMC-related issues that were evaluated or discussed with the applicant at meetings during development under I76397 are

limited. The only CMC related comments that were sent to the sponsor were in the letter of 29-JUL-2011, and these do not cover any critical issues but address format and data-related support to be included in the NDA. The applicant appears to have complied with what had been requested in that response.

FILING REVIEW CHECKLIST

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	**Yes**	**No**	**Comment**
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		For the pages that were examined for this IQA review.
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		See details outlined above.

B. FACILITIES*				
*	**If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.**			
	Parameter	**Yes**	**No**	**Comment**
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		See Form 356h
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? **This question is not applicable for synthesized API.**			NA

	Parameter	Yes	No	Comment
7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)		X	CMC information for the olodaterol API is provided by reference to BI's N203108; CMC information for the tiotropium API is provided by reference to BI's DMF 21939
8.	Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		

	Parameter	Yes	No	Comment
9.	Are additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		For those sites listed on the Form 356h

C. ENVIRONMENTAL ASSESMENT				
	Parameter	**Yes**	**No**	**Comment**
11.	Has an environmental assessment or claim of categorical exclusion been provided?	X		A categorical exclusion is requested as per 21 CFR 25.31.

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
12.	Does the section contain a description of the DS manufacturing process?			Reference is made to BI's N203108 and DMF 21939
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?			Reference is made to BI's N203108 and DMF 21939
14.	Does the section contain information regarding the characterization of the DS?			Reference is made to BI's N203108 and DMF 21939
15.	Does the section contain controls for the DS?			Reference is made to BI's N203108 and DMF 21939
16.	Has stability data and analysis been provided for the drug substance?			Reference is made to BI's N203108 and DMF 21939
17.	Does the application contain Quality by Design (QbD) information regarding the DS?			Reference is made to BI's N203108 and DMF 21939
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?			Reference is made to BI's N203108 and DMF 21939

E. DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?		X	Six executed batch records are provided, but no master batch records. As this is a 505(b)(1) application, a master batch record is not necessarily required, as long as the description of the manufacturing process is "comparably" detailed to that which would be in a master batch record. The reviewer will need to evaluate if that is the case.
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		See P.2; whether there is adequate linkage is a clinical/clinical pharmacology consideration, not a CMC consideration.
23.	Have any biowaivers been requested?		X	
24.	Does the section contain description of to-be-marketed container/closure system and presentations?	X		Note the (b) (4) device is already approved for use as part of the applicant's Combivent Respimat drug product of N21547.
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		However, it does not appear that statistical analyses of the data are included in the stability summary reports. The main trend observed is the degradation of the tiotropium drug substance.
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

F. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
29.	Is there a methods validation package?	X		

G. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product	X		The P.2. section includes a section entitled "Microbiological Attributes."

H. MASTER FILES (DMF/MAF)				
	Parameter	**Yes**	**No**	**Comment**
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
21939	2	Boehringer Ingelheim	Tiotropium Bromide Monohydrate (API)	10-SEP-2008	Found adequate to support an inhalation spray drug product 29-OCT-2008; ARs and amendments submitted subsequently
(b) (4)	3	(b) (4)		04-JUN-2012	Found adequate to support an inhalation spray drug product 13-JUN-2012; ARs and amendments submitted subsequently
	3			04-JUN-2012	Found adequate to support an inhalation spray drug product 13-JUN-2012; ARs and amendments submitted subsequently

I. LABELING				
	Parameter	**Yes**	**No**	**Comment**
32.	Has the draft package insert been provided?	X		Proposed trademarks are Stiolto™ Respimat®
33.	Have the immediate container and carton labels been provided?	X		

This document will be sequentially signed in DARRTS by all of the following who authored or reviewed this assessment:

See appended electronic signature page}
Craig M. Bertha, PhD
Acting CMC-Lead
Division III
Office of New Drug Quality Assessment

{See appended electronic signature page}
Eric Duffy, PhD
Acting Branch Chief/Division Director
Division III
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/

CRAIG M BERTHA
06/18/2014

ERIC P DUFFY
06/23/2014