CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207070Orig1s000

CHEMISTRY REVIEW(S)

NDA 207-070

Spiriva® Respimat® (tiotropium bromide) Inhalation Spray, 1.25* mcg per spray

*Expressed as tiotropium. Formulated with tiotropium bromide monohydrate (1.56 mcg per spray)

Boehringer Ingelheim Pharmaceuticals, Inc.

Eugenia M. Nashed, Ph.D.

Office of Pharmaceutical Quality (OPQ), Office of New Drug Products (ONDP), Division II, Branch IV

for

Division of Pulmonary, Allergy, and Rheumatology Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 207-070

2. REVIEW NUMBER: 1

3. REVIEW DATE: June 5, 2015

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

5. PREVIOUS DOCUMENTS: N/A

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

Submission(s) Reviewed	Document Date
Original NDA	August 15, 2014
Amendment (BC)	January 12, 2015
Amendment (BZ)	April 30, 2015
Amendment (BZ)	May 8, 2015
Amendment (BL)	May 15, 2015

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: Spiriva® Respimat®
b) Non-Proprietary Name (USAN): Tiotropium bromide inhalation spray
c) Code name/#(ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDQA only): 3 S (New formulation and new indication)

9. LEGAL BASIS FOR SUBMISSION: FD&C ACT 505(b)(1)

10. PHARMACOLOGICAL CATEGORY: Muscarinic cholinergic receptor antagonist

11. DOSAGE FORM: Oral Inhalation Spray (metered)

12. STRENGTH/POTENCY: • 1.25 mcg of tiotropium per spray from mouthpiece
(formulated with tiotropium bromide monohydrate, 1.56 mcg per spray).

Chemistry Review Data Sheet

Previously approved for COPD: • 2.5 mcg of tiotropium per spray from mouthpiece (formulated with tiotropium bromide monohydrate, 3.124 mcg per spray).

• Dose is two inhalation once daily, which corresponds to 2.5 mcg of tiotropium for the 1.25 mcg strength and to 5.0 mcg of tiotropium for the 2.5 mcg strength.

13. ROUTE OF ADMINISTRATION: Oral inhalation

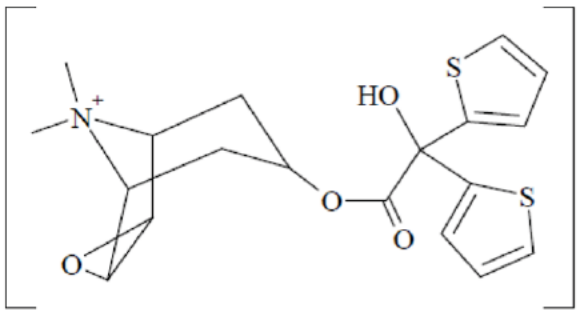
14. Rx/OTC DISPENSED: __√__Rx ___OTC

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. : $C_{19}H_{22}NO_4S_2Br \cdot H_2O$ M.W. : 490.4 (monohydrate); (b) (4)

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

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	Adequate for solution spray Inadequate for DPI (b) (4) Adequate	01-22-2015 Eugenia Nashed, PhD Review NDA 21-936 12-19-2014 Erica Englund, Ph.D. (CMC) 10-29-2008 Alan Schroeder, Ph.D. Review (b) (4)	LOA 09-10-2008 The same source for drug substance is used as in the recently approved NDAs 21-936 (2014) and 206-756 (2015). No substantial CMC changes (b) (4) (b) (4) for ds since the 2008 DMF rev.
26,014	3	Boehringer Ingelheim Pharma, GmbH & Co.KG	Container closure for Respimat aqueous solutions (b) (4)	1	Adequate Adequate	06-17-2014 Erica Englund, Ph.D. (CMC) 02-07-2013 Jessica Cole, Ph.D. (Microbiology)	LOA 06-04-2012
26,015	3	Boehringer Ingelheim Pharma, GmbH & Co.KG	Respimat inhaler device for aqueous solutions	1	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)

blue

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION
IND	46,687	Boehringer Ingelheim Pharmaceuticals, Inc.	Tiotropium bromide inhalation powder
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 31, 2004) and supplements.
NDA	203-108	Boehringer Ingelheim Pharmaceuticals, Inc.	STRIVERDI Respimat (olodaterol) inhalation spray; original NDA (dated May 14, 2012) and amendments. Approved Jul 31, 2014.
NDA	21-936	Boehringer Ingelheim Pharmaceuticals, Inc.	SPIRIVA Respimat (tiotropium bromide) inhalation spray; original NDA (dated Nov 16, 2007) and amendments. Approved Sep 24, 2014.
NDA	206-756	Boehringer Ingelheim Pharmaceuticals, Inc.	STIOLTO Respimat (tiotropium bromide and olodaterol) inhalation spray; original NDA (dated May 22, 2014) and amendments. Approved May 22, 2015.

Chemistry Review Data Sheet

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics	N/A			
EER (OPF)	Status of manufacturing and testing facilities	9/26/2014	Acceptable 06/09/2015 Linda Ng, Ph.D.	On file in Panorama
Pharm/Tox	Safety evaluation of controls for impurities, leachables and excipients	N/A	Acceptable Luqi Pei, Ph.D.	Detailed review is associated with NDA 21-936
CDRH OC	Status of device manufacturing site	7/30/2014 for NDA 206-756	Acceptable Verna/Vicenty, Ph.D.	Consult review dated 5/20/2015 is filed in DARRTS
CDRH	Engineering aspects of the Respimat device; changes since 2008.	5/06/2014 for NDA 21-936	Acceptable LeVelle/ Lakhani, Ph.D.	The same Respimat device model is used for this NDA.
Microbiology	Preservative effectiveness and microbial safety controls during manufacturing and release/stability testing	N/A	Acceptable Robert Mello, Ph.D.	Detailed review is associated with NDA 21-936. The review includes discussion of (b) (4) 1.25 mcg strengths. No significant manufacturing and control changes are reported for this NDA.
EA	Evaluation of request for Categorical Exclusion	N/A	Acceptable Alan Schroeder, Ph.D., for NDA 21-936	No changes in manufacturing scale reported for this NDA.
Method Validation	N/A			Consult not planned. Analytical methods for drug substance were reviewed under Spiriva HandiHaler (NDA 21-395). Validation for other analytical methodology addressed during reviews of NDA 21-936 and NDA 206-756.

The Chemistry Data Review for NDA 207-070

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is recommended for APPROVAL from the Chemistry, Manufacturing and Controls (CMC) team perspective. The Establishment Evaluation Report (EER) for manufacturing and testing facilities is completed on June 6, 2015, with recommendation "Acceptable" and is available on file in Panorama. The status for all Drug Master Files (DMFs) supporting this application is Adequate (refer to a summary DMF table on page 5 of this review).

Also, satisfactory recommendations from the Microbiology review team (Mello/Sweeney, 08/20/2014, for NDA 21-936), the CDRH review team (consult on the Respimat device, LeVelle/ Lakhani, 05/06/2014, for NDA 21-936), and the CDRH OC team (device manufacturing facilities, Verna/Vicenty, 05/20/2015, for NDA 206-756) are on file.

Note:

This application included data for testing two strengths of Spiriva Respimat Inhalation Spray for the treatment of asthma. The higher strength, 2.5 mcg tiotropium per spray is already approved for the treatment of COPD (NDA 21-936, 2014). Therefore, this review is focused on the CMC comparison of the lower strength, Spiriva Respimat 1.25 mcg per spray, to the already approved Spiriva Respimat 2.5 mcg per spray. All CMC data for both strengths of Spiriva Respimat are referenced to the NDA 21-936. In addition, the Applicant provided an update of the minor changes introduced to the manufacturing and control specifications for Spiriva Respimat since the approval of NDA 21-936 (amendment dated April 30, 2015), and updated labeling for the 1.25 mcg strength (amendments dated May 8 and 15, 2015). Upon the review of all supporting data this application is considered adequate from the CMC perspective to support the approval for marketing of Spiriva® Respimat® (tiotropium bromide) Inhalation Spray, 1.25 mcg, and for the continuance of marketing the Spiriva® Respimat® (tiotropium bromide) Inhalation Spray, 2.5 mcg product~~, pending favorable recommendation from the OPF.~~

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

None

II. Summary of Chemistry Assessment

Executive Summary Section

A. Description of Drug Substance and Drug Product:

Spiriva® Respimat® (tiotropium bromide) Inhalation Spray is a drug-device combination product consisting of a plastic/aluminum cartridge containing sterile aqueous formulation of tiotropium bromide and a Respimat delivery device, which was developed by Boehringer Ingelheim (BI). Spiriva Respimat (tiotropium bromide) Inhalation Spray is proposed for treatment of asthma. Two strengths of drug product, 1.25 mcg and 2.5 mcg of tiotropium per spray, were used in the pivotal clinical trials supporting this application. The 2.5 mcg strength was approved for treatment of COPD (NDA 21-936, 2014) and the 1.25 mcg strength is considered for approval under this NDA.

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, 2.5 mcg (NDA 21-936, 2014). The Respimat device is approved since 2011 as an integral part of Combivent Respimat (ipratropium bromide/albuterol) Inhalation Spray (NDA 21-747) for treatment of COPD. Three additional NDAs from BI with Respimat containing drug products are approved for marketing for treatment COPD as follow: Spiriva Respimat (tiotropium bromide) Inhalation Spray, 2.5 mcg (NDA 21-936, 2014), (Striverdi Respimat (olodaterol) Inhalation Spray (NDA 203-108, 2014), and Stiolto Respimat (tiotropium bromide/olodaterol) Inhalation Spray (NDA 206-756, 2015).

The drug product is manufactured by Boehringer Ingelheim in Germany and supplied as co-packaged set of one cartridge and one Respimat inhaler, with color coded cartridge label and device cap. Light blue (sky blue) color is used for the 1.25 mcg of tiotropium per spray strength, and aqua color is used (as approved under NDA 21-936) for the 2.5 mcg of tiotropium per spray strength.

The drug product formulations are aqueous based, sterile and contained in a sealed cartridge. The 1.25 mcg strength contains (b) (4) tiotropium bromide monohydrate) (b) (4) formulation contains (b) (4) of benzalkonium chloride (b) (4) of edetate sodium (b) (4) and hydrochloric acid (b) (4)

The Respimat inhaler produces an aerosol by mechanical means; there is 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 1.25 mcg (b) (4) of tiotropium (b) (4) spray volume. A dose is comprised of two actuations, i.e., 2.5 mcg (b) (4) The Respimat device contains an actuation counter. The commercial device delivers 60 actuations (30 doses) after priming (b) (4) . Also, there is a physician sample version which delivers 28 actuations (14 doses) after priming. The physician sample has the same fill as the commercial product however the lock mechanism engages sooner to prevent further actuations.

The drug substance, tiotropium bromide monohydrate is a white (b) (4) powder which is slightly soluble in water (b) (4) and methanol (b) (4) It is practically insoluble in (b) (4) No polymorphic form are known (b) (4)

Tiotropium bromide is a (b) (4). It is supported by DMF 21,939, which has an adequate status as summarized in the DMF table on page 5 of this review.

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

Spiriva® Respimat® (tiotropium bromide) Inhalation Spray is a multidose drug-device combination product for the long-term maintenance treatment of patients with asthma. A once-daily treatment comprises of two inhalations from the mouthpiece of Respimat inhaler for a total of 2.5 mcg of tiotropium.

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 blue-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°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. The 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 drug product. Also, 36 months of the real time stability data for 9 batches of the higher strength of Spiriva Respimat, (b) (4) per spray, is available and it is supportive of the 36 months expiry period.

The in use expiry (after the cartridge is inserted into inhaler) is 3 months, and it is supported by the in-use stability data for both strengths of the drug product..

C. Basis for Approvability Recommendation

Not applicable. The application is recommended for approval from the CMC perspective.

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	• Quantities formulated are checked by second person • Final drug product specification includes tests for both formulation assays and SCU • The applicant checks the cartridge fill mass at the (b) (4) cartridges; each cartridge is weight checked by balance (b) (4) • See referenced DMF 26015 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 • There is a 100% vacuum test performed (b) (4) during manufacture to detect and reject any cartridges that are not sealed • 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) • (b) (4)	2	2	2	8	• Assay and physicochemical properties of formulation (viscosity/surface tension) are assured by control of the solution composition (quantities formulated are checked by second person) • The applicant claims (b) (4) ee referenced DMF 26015 (also note device already approved for applicant's drug product of N21747, N21936 and N203108 • The applicant checks the cartridge fill mass at the (b) (4) cartridges; each cartridge is weight checked by balance (b) (4) • Applicant provides data in the justification of specifications section to support use (b) (4) 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 in-process test and acceptance criteria for the formulation pH • There is a 100% vacuum test performed (b) (4) during manufacture to detect and reject any cartridges that are not sealed • 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

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

See appended electronic signature page}
Eugenia M. Nashed, PhD
CMC Reviewer
Branch IV, Division II
Office of New Drug Products

Eugenia M. Nashed -S
Digitally signed by Eugenia M. Nashed -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300102452, cn=Eugenia M. Nashed -S
Date: 2015.06.09 16:14:05 -04'00'

{See appended electronic signature page}
Julia Pinto, PhD
Acting Branch Chief
Branch IV, Division II
Office of New Drug Products

Julia C. Pinto -A
Digitally signed by Julia C. Pinto -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Julia C. Pinto -A, 0.9.2342.19200300.100.1.1=1300366849
Date: 2015.06.09 16:19:34 -04'00'

Cc:
Craig M. Bertha, PhD
CMC Lead
Branch IV, Division II
Office of New Drug Products

Eric Duffy, PhD
Division Director
Division II, Office of New Drug Products
Office of Pharmaceutical Quality (OPQ)

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

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

A. Labeling & Package Insert

The comments on the CMC portion of the label are provided directly to the working copy of the package insert during team meetings. The lack of dose proportionality between the 1.25 mcg Spiriva Respimat (under this NDA) and the 2.5 mcg Spiriva Respimat (approved under NDA 21-936) was discussed with the review team during WU meeting on May 28, 2015. The importance of dose delivery as 2 sprays will be considered by the review team during the labeling discussions.

Name and Description:

SPIRIVA RESPIMAT (tiotropium bromide) Inhalation Spray is a drug-device combination product.

How Supplied:

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

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

The SPIRIVA 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. (b) (4) The written information on the label of the gray inhaler body indicate that it is labeled for use with the SPIRIVA RESPIMAT cartridge (b) (4).

SPIRIVA RESPIMAT Inhalation Spray: 60 metered actuations (NDC 0597-0160-61)
SPIRIVA RESPIMAT Inhalation Spray: 28 metered actuations (NDC 0597-0160-31) ((b) (4))

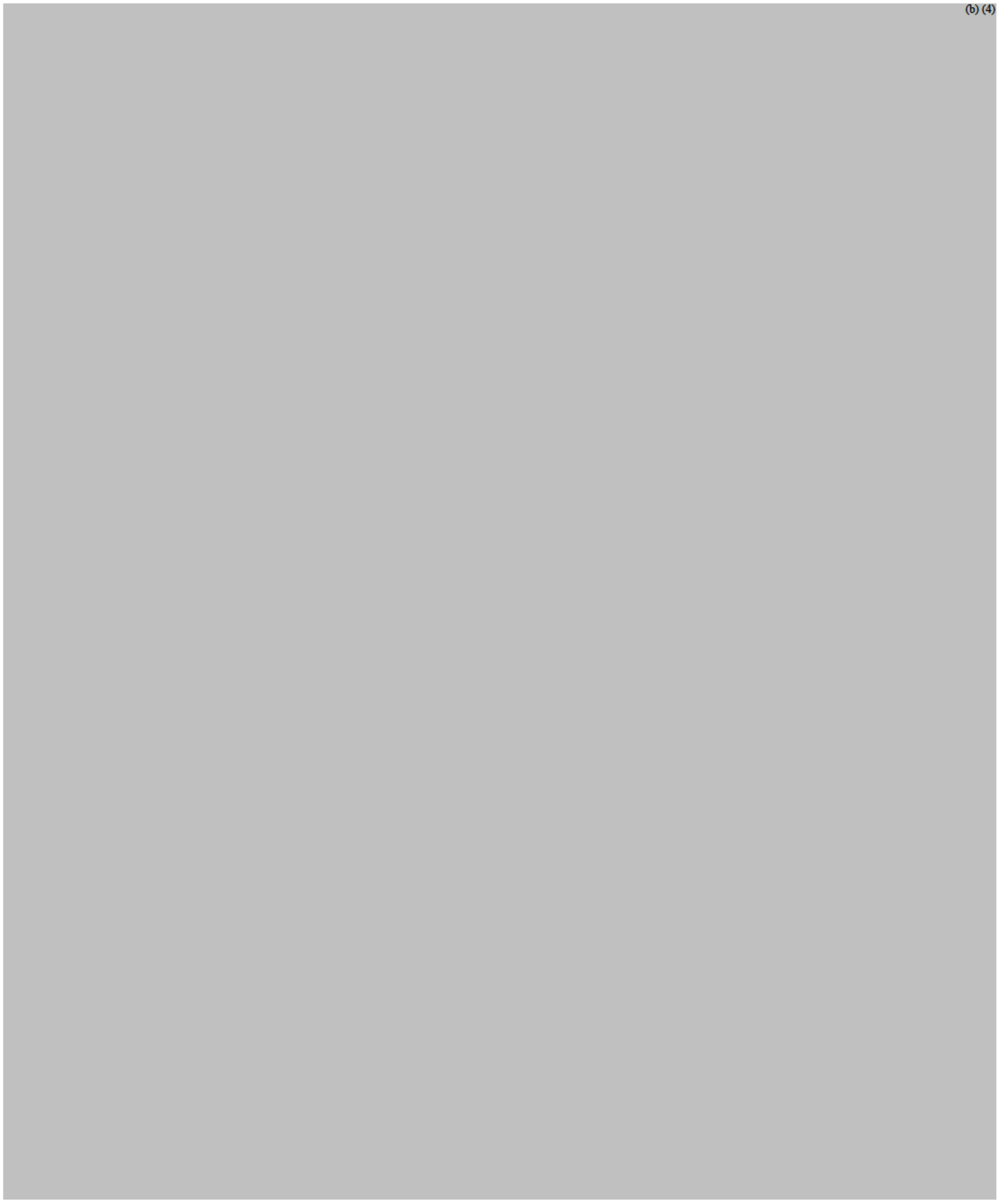
(b) (4)
Distributed by:
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, CT 06877 USA

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 the container and carton labels are reproduced below for a reference.

(b) (4)



(b) (4)

B. Environmental Assessment or Claim of Categorical Exclusion

The Applicant applied for categorical exclusion under 21 CFR 25.31(b), which was evaluated and considered adequate during the review of NDA 21-936. Refer to CMC review by Dr. Eugenia Nashed, dated July 25, 2014.

III. List of CMC Deficiencies and Comments

CMC Comments Communicated to the Applicant in IR letter dated January 6, 2015

Provide additional information, including the product label, on the salmeterol HFA MDI product used as a comparator in clinical trials 205.418, 205.419 and 205.342. Include the composition and dose delivery (i.e., content of salmeterol base from the valve and from the actuator) of the salmeterol product used in your trials compared to the previously US-approved Serevent (salmeterol xinafoate) CFC metered dose inhalation product. Provide any available information and data on the comparison of dose characteristics for the HFA based product in comparison to the CFC based product.

CMC Comments Communicated to the Applicant in IR letter dated April 24, 2015

Your submission dated August 15, 2014, to NDA 207070, is currently under review. Also, refer to the teleconference with the Agency on April 20, 2015. We have the following requests for information. If these data were previously submitted, provide the submission date.

1. Briefly summarize what is the same between the 1.25 mcg and 2.5 mcg products, e.g., manufacturing, components, device, etc. Specify any changes implemented to either product since the approval of NDA 21936.

2. List (b) (4) supporting data, i.e., either submit the data as Appendix or provide detailed references to prior submissions.

   Address the following items:

   a. Formulations, including different ratio of API to other components

   b. Stability data supporting proposed expiry for 1.25 mcg product

   c. In-use stability period and supporting data for 1.25 mcg product

   d. (b) (4)

3. Provide current Specifications and Stability Protocol for the 1.25 mcg product and specify any differences from the prior versions.

4. Submit revised container closure labeling to clearly distinguish between the 1.25 mcg and 2.5 mcg products.

5. Briefly summarize differences between the total dose of medication received by the patient when administered as 2 actuations (puffs) of 1.25 mcg product *versus* 1 actuation of 2.5 mcg product.

CMC Comments for the Action Letter

None.

There are no holding comments for this NDA from the CMC perspective. The labeling comments will be addressed during the labeling discussions with Applicant as deemed necessary by the review team.

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

/s/

EUGENIA M NASHED

06/11/2015

This is duplicate version of my signed review that was uploaded to Panorama on 06/09/15, however it is not accessible to view until now. ERIC ticket is pending.

Overall Manufacturing Inspection Recommendation

Task Summary | Task Details | Issues | Updates | **Inspection Management Form**

Inspection Management Form As of 2:29 PM

Inspection Management Form

NDA 207070-Orig1-New/NDA(1)

(b) (4) **CTL CONTROL TESTING LABORATORY | Approve Facility -** (b) (4)

BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG | 3002806556 | (b) (4) **AEROSOL DISPERSED MEDICATION | Approve Facility - 2016-03-07**

BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG | 3002806556 | (b) (4)

(b) (4) **| Approve Facility - 2017-03-07**

BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG | 3002806556 | (b) (4) **DEVICE KIT ASSEMBLER | Approve Facility - 2017-03-07**

(b) (4)

Overall Manufacturing Inspection Recommendation

- Approve
- Withhold

Overall Application Re-evaluation Date

1/28/16

Cancel

Assigned To

OPF Reviewer

Linda Ng

Edit Assignment

This was done on

Jun 9, 2015

(Today)

Status

Complete

This task is waiting on

2 Tasks

Last Update	Submitted On
Jun 9, 2015	Sep 30, 2014

Reference Number

2371769

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 Number: NDA 207070
   Submission Date: August 15, 2014
   21st C. Review Goal Date: April 15, 2015
   PDUFA Goal Date: June 15, 2015

3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	SPIRIVA® RESPIMAT®
Established or Non-Proprietary Name (USAN) and strength:	Tiotropium bromide inhalation spray
Dosage Form:	Inhalation spray

4. SUBMISSION PROPERTIES:

Review Priority :	STANDARD
Applicant Name:	BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.
Responsible Organization (OND Division):	DPARP

II. Application Detail

1. INDICATION: Bronchodilator indicated for the long-term, once-daily, add-on maintenance treatment of asthma in patients 12 years of age and older who remain symptomatic on at least inhaled corticosteroids

2. ROUTE OF ADMINISTRATION: Oral Inhalation

3. STRENGTH/POTENCY: (b) (4)

4. Rx/OTC DISPENSED: x☐Rx ☐OTC

5. ELECTRONIC SUBMISSION (yes/no)? yes

6. 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			
9.	Complex manufacturing				
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 #?	X		
	2. Do comments in EES indicate a request to participate on inspection(s)?		X	
	3. Is this first application by the applicant?		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	
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?			None
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	All information referred to NDA 21-936

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	(b) (4) product in previous NDA 21-936; this is for different indication.

Include process flow chart/diagram (see eCTD Section 2.3.P.1)
No flow chart provided for process manufacturing of the drug product in this NDA. The

product (b) (4) NDA 21-936 but for different indication; product intended for the COPD indication..

Table 2 Composition of Spiriva® Respimat® Inhalation Spray (Mass per dose)

Strength	(b) (4)	1.25 µg per actuation	2.5 µg per actuation	(b) (4)	Placebo
Name of ingredient		Mass per dose [mg]			
Tiotropium (corresponds to tiotropium bromide monohydrate [1])		0.0025 (0.0031)	0.0050 (0.0062)		0
Benzalkonium chloride		(b) (4)			(b) (4)
Edetate disodium					
(b) (4) Hydrochloric acid					
Water for injections					
Commercial Formulation					

(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

4. **Drug Product Facility Inspectional History that could impact the manufacturing of this product.** None. The NDA drug product in NDA 21-936 has received an overall AC EES recommendation on 9/11/2014 and has been approved.

Additional information not covered above None

Manufacturing Facilities Chart (generated from 602A DARRTS report and OMPQ macro):

Fpr 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.**

NDA:	**207070 TIOTROPIUM BROMIDE**
Sponsor:	**BOEHRINGER INGELHEIM PHARMACEUTICALS INC**
Indication:	**Treatment of asthma for those who remain symptomatic on at least inhaled corticosteroids**
PDUFA:	**6/15/2015 under STANDARD Review**
Responsible Organization:	**CDER/ODEII/DPARP**
EERS Submitted By:	
Chart Generated On:	**9/26/2014**
	Overall OC Recomendation: **entered into EES on**
	Reevaluation date:

Establishment Name	EER Creation Date	FEI Num	District Short	Country Code	Responsibilities	Profile Code	Firm Profiles - Current Status	Inspection History, Dates, Classifications	Comment
(b) (4)									
BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG	9/17/2014	3002806556	EEU	DEU	Drug Product manufacturing; analyical testing	ADM	http://intranetapps.fda.gov/scripts/mpqa/profile.cfm?FEI=3002806556	Acceptable in inspection 3/14/2014 (b) (4)	
(b) (4)									
BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG	9/17/2014	3002806556	EEU	DEU	Drug Product manufacturing; pacaging & labeling; analyical testing	CSN	http://intranetapps.fda.gov/scripts/mpqa/profile.cfm?FEI=3002806556	Inspection for 3/17/2014 was AC (b) (4)	
(b) (4)									

V. Overall Conclusions and Recommendations

Is the application fileable? (yes/no, Yes to questions 11-12) Yes. Drug product (b) (4) approved NDA 21-936 but different indication.
Based on Section IV, is a KTM warranted for any PAI? (yes/no). If yes, please identify the sites in the above chart. No
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
11/05/2014

MAHESH R RAMANADHAM
11/24/2014

IQA and Filing Review Cover Sheet

1. NEW DRUG APPLICATION NUMBER: NDA 207-070

2. DATES AND GOALS:

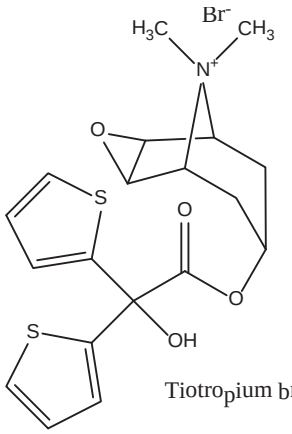
Letter Date: 15-AUG-2014	Submission Received Date : 15-AUG-2014
PDUFA Goal Date: 15-Jun-2015	

3. PRODUCT PROPERTIES:

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

4. INDICATION: For long-term, once-daily maintenance treatment of asthma in patients 12 years and older who remain symptomatic on at least inhaled corticosteroids.

5. DRUG SUBSTANCE STRUCTURAL FORMULAE:



Tiotropium bromide

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

7. SUBMISSION PROPERTIES:

Review Priority:	Standard
Submission Classification (Chemical Classification Code):	New Indication (for tiotropium)
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		X	
Clinical Pharmacology		X	
Establishment Evaluation Request (EER)	X		The submission of the EER to Office of Compliance is pending.
Pharmacology/Toxicology		X	
Methods Validation		X	The analytical methods are the same as for NDA 21-936, approved September 2014.
Environmental Assessment		X	The applicant claims categorical exclusion as per 21 CFR 25.31, which was evaluated under NDA 21-936 and found acceptable.
CDRH		X	It is noted that the Respimat® device is already approved for the Combivent® drug product of N20291 and N21936.
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):
None

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

ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications

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	• Quantities formulated are checked by second person • Final drug product specification includes tests for both formulation assays and SCU • The applicant checks the cartridge fill mass at the (b) (4) cartridges; each cartridge is weight checked by balance (b) (4) d • See referenced DMF 26015 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 • There is a 100% vacuum test performed (b) (4) during manufacture to detect and reject any cartridges that are not sealed • 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)	2	2	2	8	• Assay and physicochemical properties of formulation (viscosity/surface tension) are assured by control of the solution composition (quantities formulated are checked by second person) • The applicant claims (b) (4) see referenced DMF 26015 (also note device already approved for applicant's drug product of N21747 (Combivent Respimat) • The applicant checks the cartridge fill mass at the (b) (4) cartridges; each cartridge is weight checked by balance (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 (b) (4) 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 in-process test and acceptance criterion for the formulation pH • There is a 100% vacuum test performed (b) (4) during manufacture to detect and reject any cartridges that are not sealed • 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

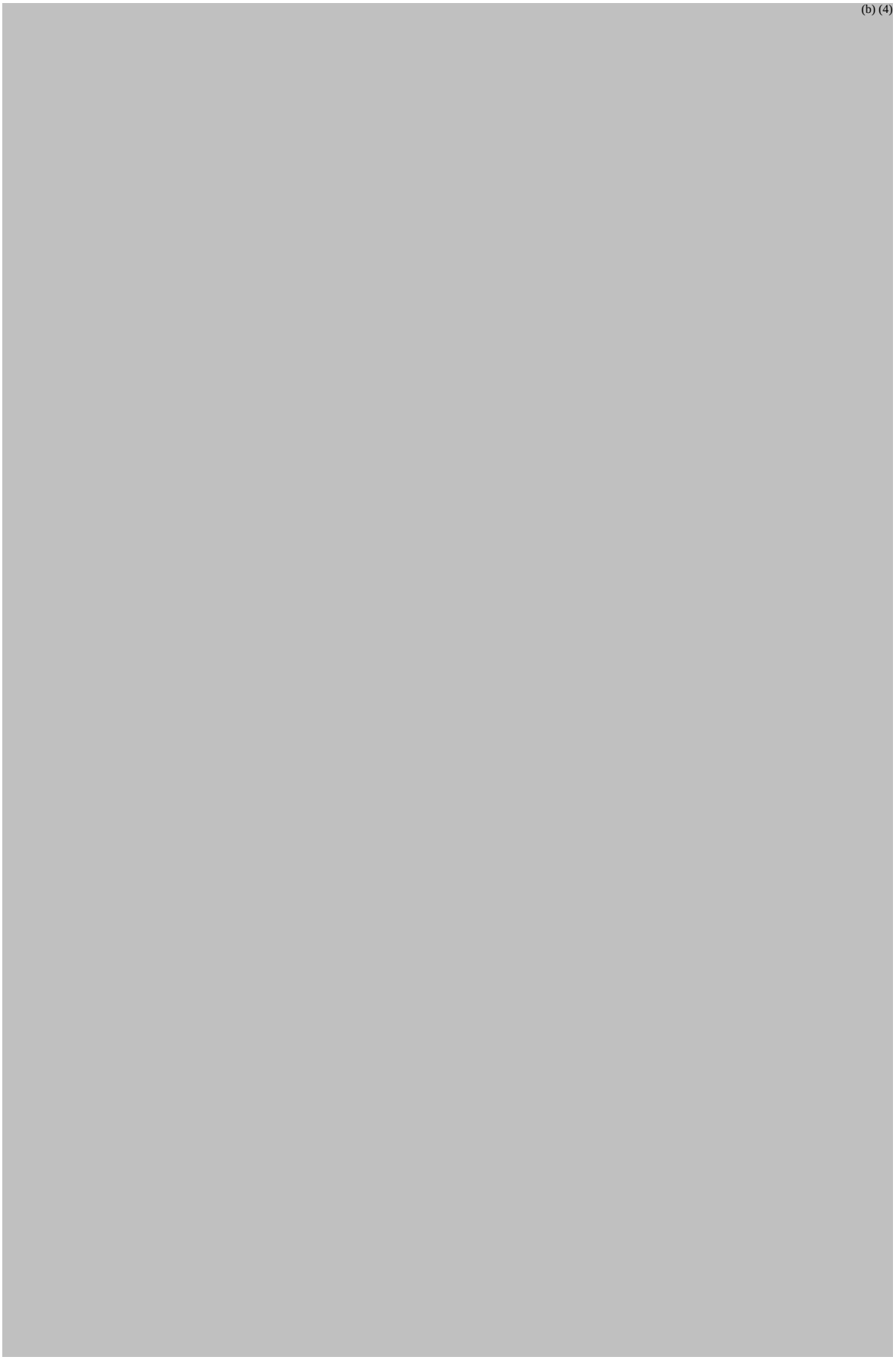
The applicant has previously submitted application for the same drug product indicated for the treatment of COPD, NDA 21-936. The application was approved on September 24, 2014. All CMC data supporting this NDA are referenced to NDA 21-936. The CMC review will focus on the clinical trial formulations and batches used in clinical studies supporting this NDA (asthma indication). Refer to summary provided in Tables 1-23, and submitted in section 3.2.P.2 of the NDA submission.

The drug product prepared with the tiotropium bromide drug substance 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 (b) (4) to generate an aerosol of the formulation. Each actuation delivers (b) (4) of tiotropium (as the cation). Daily dose consists of two actuations (b) (4) There are two presentations for the drug product, a trade presentation that delivers 60 actuations and a physician sample presentation that delivers 28 actuations. Both of these have identical fills but lock out at different points. 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 limited to 3 months. The following figures from the proposed labeling show two views of the device and the cartridge.

Start of Applicant Material

End of Applicant Material

(b) (4)



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		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		

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		
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 N21936
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?			Reference is made to BI's N21936
14.	Does the section contain information regarding the characterization of the DS?			Reference is made to BI's N21936
15.	Does the section contain controls for the DS?			Reference is made to BI's N21936
16.	Has stability data and analysis been provided for the drug substance?			Reference is made to BI's N21936
17.	Does the application contain Quality by Design (QbD) information regarding the DS?			Reference is made to BI's N21936
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?			Reference is made to BI's N21936

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		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		Reference is made to BI's N21936
23.	Have any biowaivers been requested?		X	
24.	Does the section contain description of to-be-marketed container/closure system and presentations?	X		Reference is made to BI's N21936
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		Reference is made to BI's N21936
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		Reference is made to BI's N21936

G. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product	X		Reference is made to BI's N21936

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
26014	3	Boehringer Ingelheim	Container Closure for RESPIMAT Aqueous Solutions	04-JUN-2012	Found adequate to support an inhalation spray drug product 13-JUN-2012; ARs and amendments submitted subsequently
26015	3	Boehringer Ingelheim	RESPIMAT Inhaler for Aqueous Solutions	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 Spiriva™ Respimat®
33.	Have the immediate container and carton labels been provided?	X		

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

See appended electronic signature page}
Eugenia M. Nashed, PhD
Senior CMC Reviewer
Branch VIII, Division III
Office of New Drug Quality Assessment

eugenia.nashed@fda.hhs.gov
Digitally signed by eugenia.nashed@fda.hhs.gov
DN: cn=eugenia.nashed@fda.hhs.gov
Date: 2014.10.16 15:17:09 -04'00'

{See appended electronic signature page}
Julia Pinto, PhD
Acting Branch Chief
Branch VIII, Division III
Office of New Drug Quality Assessment

Julia C. Pinto -A
Digitally signed by Julia C. Pinto -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Julia C. Pinto -A, 0.9.2342.19200300.100.1.1=1300366849
Date: 2014.10.16 15:28:33 -04'00'

Cc:
Craig M. Bertha, PhD
Acting CMC-Lead
Branch VIII, Division III
Office of New Drug Quality Assessment