

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
021936Orig1s000

CHEMISTRY REVIEW(S)

CMC Review Amendment (Finalized GMP Inspection)

Date	September 18, 2014
From	Eugenia M. Nashed, Ph.D.
Subject	CMC Review Amendment
NDA	NDA 21-936
Applicant	Boehringer-Ingelheim
Date of Submission	March 24, 2014 (Resubmission)
PDUFA Goal Date	September 24, 2014
Proprietary Name / Established (USAN) name	Spiriva Respimat/ tiotropium inhalation spray
Dosage forms / Strength	Inhalation Spray / 2.5 mcg per spray (expressed as tiotropium)
Proposed Indication	Once daily maintenance treatment of bronchospasm associated with COPD and for reduction of COPD exacerbations
Recommended:	Approval

At the conclusion of Chemistry Review #3, dated July 23, 2014, the CMC team recommended approval pending acceptable recommendations from the (A) Office of Compliance, the (B) OPS Microbiology review team and the (C) CDRH device review teams. At the present time all pending issues have been successfully resolved and the Chemistry review team recommends APPROVAL for NDA 21-936, from the CMC perspective. Refer, to point-by-point updates listed below, to the CMC-related activities which took place since the last review filing.

A. Establishment Evaluation Report (EER)

An acceptable overall recommendation is available for NDA 21-936 as of September 11, 2014. Refer to copy of detail report attached at the end of this review amendment.

B. Microbiology Recommendation

A review from the OPS New Drug Microbiology team (Drs. R. Mello and N. Sweeney) with acceptable recommendation for approval is filed in DARRTS on August 22, 2014.

C. CDRH Device Consults

The Spiriva Respimat Inhalation Spray is a drug-device combination product and two consults were forwarded to CDRH, as follows:

1. Consult to CDRH/DAGRID/Combination Products, dated May 6, 2014, to review the engineering aspects of the Respimat device, in particular changes introduced to the device since the first review cycle in 2008, and
2. Consult to CDRH/Office of Compliance, dated May 20, 2014, to determine whether an inspection is necessary at the device manufacturing sites (b) (4).

The CDRH Combination Products team (Drs. LeVelle and Lakhani) requested additional information from the Applicant on July 14, 2014, and upon review of the response, recommends acceptable status of device functionality for the NDA approval – refer to review dated August 21, 2014, filed into DARRTS.

The CDRH Office of Compliance team (Drs. Vuniqi and Vincenty) could not reach the final decision regarding the inspection due to the missing documentation (CFR 820), however during join meeting between the ONDQA, Office of Combination Products (OCP), CDER/OC and the CDRH/OC (September 11, 2014), it was determined that the above review issues should not hold an approval of this NDA. A consideration was given to the fact that two applications from Boehringer Ingelheim had already been approved by the Agency (N21-747 and N203-108), and that these used the identical drug delivery device, Respimat A5, which is marketed since 2011. Also, another two NDA applications with Respimat A5 device are currently pending (206-756 and (b) (4)), which creates an opportunity to address the potential device deficiencies during the review of these products.

CMC Review Amendment
 NDA 21-936 Spiriva (tiotropium) Inhalation Spray, 2.5 mcg per spray
 Eugenia M. Nashed, Ph.D.

Attachment (EER Report)

**FDA CDER EES
 ESTABLISHMENT EVALUATION REQUEST
 DETAIL REPORT**

Application:	NDA 21936/000	Action Goal:	
Stamp Date:	16-NOV-2007	District Goal:	26-JUL-2014
Regulatory:	24-SEP-2014		
Applicant:	BOEHRINGER PHARMS 900 RIDGEBURY RD RIDGEFIELD, CT 068770368	Brand Name:	SPIRIVA RESPIMAT
		Estab. Name:	
		Generic Name:	TIOTROPIUM BROMIDE INHALATION SPRAY
Priority:	3S	Product Number; Dosage Form; Ingredient; Strengths	
Org. Code:	570		001; SPRAY; TIOTROPIUM BROMIDE; 2.5UGM

Application Comment: THIS NDA IS THE FIRST INHALATION SPRAY DOSAGE FORM. THE INHALATION SPRAY DELIVERS 2.5 MICROGRAM/ACTUATION OF TIOTROPIUM BROMIDE. THIS IS FOR ORAL INHALATION ONLY. NOTE THAT THE APPLICANT ALSO LISTED TWO ADDITIONAL SITES (b) (4)
 (b) (4) THEY ALSO LIST BOEHRINGER INGELHEIM MICROPARTS GMBH, HAUERT 7, 44227 DORMUND, GERMANY AS RESPONSIBLE FOR ALTERNATE TESTING SITE FOR THE RESPIMAT INHALER. THESE TWO SITES WERE NOT ENTERED INTO EES UPON THE RECOMMENDATIONS OF SHAWNTE ADAMS (IN AN EMAIL) STATING THAT THEY WILL NOT BE INSPECTED. THE CONTACT PERSON FOR THE (b) (4) WILL BE REQUESTED AND UPDATED IN EES. (on 20-DEC-2007 by PERIP)

FDA Contacts:	E. NASHED	Prod Qual Reviewer	(HFD-820)	3017961723
	Y. LIU	Product Quality PM		3017961926
	J. LEE	Regulatory Project Mgr		3017963769
	C. BERTHA	Team Leader		3017961646

Overall Recommendation:	ACCEPTABLE	on 11-SEP-2014	by J. WILLIAMS	()	3017964196
	PENDING	on 11-SEP-2014	by EES_PROD		
	ACCEPTABLE	on 11-SEP-2014	by T. SHARP	()	3017963208
	PENDING	on 06-FEB-2013	by EES_PROD		
	PENDING	on 23-DEC-2011	by EES_PROD		
	WITHHOLD	on 22-AUG-2011	by EES_PROD		
	ACCEPTABLE	on 07-MAR-2008	by EES_PROD		

CMC Review Amendment
 NDA 21-936 Spiriva (tiotropium) Inhalation Spray, 2.5 mcg per spray
 Eugenia M. Nashed, Ph.D.

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

Establishment Comment: THIS SITE IS RESPONSIBLE FOR ALL ASPECTS OF MANUFACTURING, PACKAGING, AND CONTROL OPERATIONS FOR TIOTROPIUM BROMIDE DRUG SUBSTANCE. IT IS ALSO RESPONSIBLE FOR ALL ASPECTS OF MANUFACTURING, PACKAGING AND CONTROL FOR SPIRIVA RESPIMAT INHALATION SPRAY (on 20-DEC-2007 by PERIP)

Profile:	AEROSOL DISPERSED MEDICATION	OAI Status:	NONE
	NON-STERILE API BY CHEMICAL SYNTHESIS		NONE
	DEVICE KIT ASSEMBLER		NONE
	SUBMITTED TO OC	31-JAN-2008	PERIP
	SUBMITTED TO DO	05-FEB-2008 GMP Inspection	ADAMSS
	DO RECOMMENDATION	07-MAR-2008	ACCEPTABLE ADAMSS
	OC RECOMMENDATION	07-MAR-2008	ACCEPTABLE ADAMSS
	SUBMITTED TO OC	02-APR-2014	LIUY
	SUBMITTED TO DO OAI PDUFA GOAL DATE: 24-SEP-2014	15-APR-2014 10-Day Letter	SAFAAUJAZIR
	UNDER REVIEW	17-APR-2014	PHILPYE
	DO RECOMMENDATION	02-JUN-2014	ACCEPTABLE PHILPYE
	OC RECOMMENDATION	10-JUN-2014	ACCEPTABLE IYERS
	SUBMITTED TO OC	20-DEC-2007	PERIP
	SUBMITTED TO DO	20-DEC-2007 GMP Inspection	ADAMSS
	DO RECOMMENDATION	31-JAN-2008	ACCEPTABLE ADAMSS
	OC RECOMMENDATION	31-JAN-2008	ACCEPTABLE ADAMSS
	SUBMITTED TO OC	02-APR-2014	LIUY
	SUBMITTED TO DO POAL PDUFA GOAL DATE: 24-SEP-2014	07-APR-2014 10-Day Letter	SAFAAUJAZIR
	DO RECOMMENDATION	11-APR-2014	WITHHOLD PHILPYE
	SUBMITTED TO DO CSN PROFILE NOW AC.	26-AUG-2014 10-Day Letter	WILLIAMSJU
	DO RECOMMENDATION	27-AUG-2014	ACCEPTABLE MROSE
	OC RECOMMENDATION	28-AUG-2014	ACCEPTABLE WILLIAMSJU
	SUBMITTED TO OC	11-SEP-2014	LIUY
	OC RECOMMENDATION CDRH/OC RECOMMENDS A POST-APPROVAL INSPECTION WITHIN 6 MONTHS OF PDUFA.	11-SEP-2014	ACCEPTABLE WILLIAMSJU

CMC Review Amendment
 NDA 21-936 Spiriva (tiotropium) Inhalation Spray, 2.5 mcg per spray
 Eugenia M. Nashed, Ph.D.

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

DMF No: AADA:

Responsibilities: FINISHED DOSAGE RELEASE TESTER
 FINISHED DOSAGE STABILITY 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	02-APR-2014				LIUY
SUBMITTED TO DO	03-APR-2014	Product Specific and GMP Inspection			IYERS
DO RECOMMENDATION	11-APR-2014	SHOULD NOT HAVE BEEN PS+GMP - NOT NEW PROFILE		ACCEPTABLE	PHILPYE
OC RECOMMENDATION	15-APR-2014			ACCEPTABLE	SAFAAJAZIR

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

DMF No: AADA:

Responsibilities: FINISHED DOSAGE STERILITY TESTER

Establishment Comment: THIS SITE IS AN ALTERNATE TESTING SITE FOR MICROBIOLOGICAL TESTING (b) (4). NO SITE INFORMATION OR CONTACT INFORMATION IS PROVIDED FOR THIS SITE. THE APPLICANT CLAIMS THAT THE FEI NUMBER FOR HIS SITE IS (b) (4). HOWEVER THIS SITE DID NOT MATCH WITH EES RECORDS. IN AN EMAIL FROM SHAWNTE ADAMS, A CORRECT CFN FOR THE SITE WAS OBTAINED AND ENTERED AS (b) (4) ON 20-DEC-2007 BY PERIP

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	20-DEC-2007				PERIP
SUBMITTED TO DO	20-DEC-2007	GMP Inspection			ADAMSS
DO RECOMMENDATION	31-JAN-2008			ACCEPTABLE	ADAMSS
OC RECOMMENDATION	31-JAN-2008			ACCEPTABLE	ADAMSS
SUBMITTED TO OC	02-APR-2014				LIUY
OC RECOMMENDATION	04-APR-2014			ACCEPTABLE	SAFAAJAZIR

CMC Review Amendment
 NDA 21-936 Spiriva (tiotropium) Inhalation Spray, 2.5 mcg per spray
 Eugenia M. Nashed, Ph.D.

Establishment: CFN: [REDACTED] FEI: (b) (4)

DMF No: [REDACTED] AADA:

Responsibilities: [REDACTED] (b) (4)
 FINISHED DOSAGE STERILITY TESTER

Establishment Comment: [REDACTED] (b) (4) DRUG PRODUCT: (STERILITY TESTING), (on 02-APR-2014 by Y. LIU (J) 3017961926)

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
<u>Comment</u>					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
<u>Reason</u>					
SUBMITTED TO OC	02-APR-2014				LIUY
SUBMITTED TO DO	03-APR-2014	Product Specific and GMP Inspection			IYERS
DO RECOMMENDATION	11-APR-2014			ACCEPTABLE	MROSE
OC RECOMMENDATION	18-APR-2014			ACCEPTABLE	SAFAAJAZIR

Establishment: CFN: [REDACTED] FEI: (b) (4)

DMF No: [REDACTED] AADA:

Responsibilities: FINISHED DOSAGE LABELER
 FINISHED DOSAGE PACKAGER

Establishment Comment:

Profile: AEROSOL DISPERSED MEDICATION OAI Status: NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
<u>Comment</u>					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
<u>Reason</u>					
SUBMITTED TO OC	02-APR-2014				LIUY
SUBMITTED TO DO	04-APR-2014	Product Specific and GMP Inspection			SAFAAJAZIR
FIRST FDA EVALUATION OF ESTABLISHMENT. PDUFA GOAL DATE:24-SEP-2104					
ASSIGNED INSPECTION TO IB	06-MAY-2014	Product Specific and GMP Inspection			KCULVER
INSPECTION PERFORMED VAI; 1 ITEM 483 ISSUED.	09-JUL-2014		09-JUL-2014		KCULVER
DO RECOMMENDATION	22-JUL-2014			ACCEPTABLE	KCULVER
INSPECTION VAI. THIS FIRM IS DOING SECONDARY PACKAGING FOR THIS PRODUCT THAT ALREADY HAS LOT NO AND EXPIRY INFO ON IT. FIRM ALSO HAS GENERAL CAPABILITY TO DO PRIMARY PACKAGING TO ADD LOT NO AND EXPIRY INFO IF NEEDED FOR OTHER CLIENTS.					
OC RECOMMENDATION	22-JUL-2014			ACCEPTABLE	SAFAAJAZIR

CMC Review Amendment
 NDA 21-936 Spiriva (tiotropium) Inhalation Spray, 2.5 mcg per spray
 Eugenia M. Nashed, Ph.D.

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

(b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE LABELER
 FINISHED DOSAGE PACKAGER

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	02-APR-2014				LIUY
SUBMITTED TO DO	04-APR-2014	Product Specific and GMP Inspection			SAFAAJAZIR
NEW DOSAGE FORM FOR ESTABLISHMENT. PDUFA GOAL DATE:24-SEP-2014					
ASSIGNED INSPECTION TO IB	09-APR-2014	Product Specific and GMP Inspection			DOMBROWSKIR
NEW FORM - PS AND GMP					
DO RECOMMENDATION	12-MAY-2014			ACCEPTABLE	DOMBROWSKIR
EI OF SITE DATED (b) (4). FOUND NAI - FIRM IS SECONDARY PACKAGER IN THIS APPLICATION - FIRM HAD AWARENESS BUT NO ACTIVE INVOLVEMENT TO DATE. STATED TO BE BACK UP SITE TO (b) OPERATION. AGAIN, SECONDARY PACKAGING ONLY.					
SUBMITTED TO DO	13-MAY-2014	10-Day Letter			RHX
PLEASE UPDATE THE MILESTONE					
DO RECOMMENDATION	15-MAY-2014			ACCEPTABLE	DOMBROWSKIR
INSPECTION DATED (b) (4). FOUND ACCEPTABLE - FIRM PERFORMS SECONDARY PACKAGING ONLY. GMP FOR SITE COMPLETED; FIRM HAD KNOWLEDGE OF APPLICATION, BUT IS ONLY EXPECTING TO SERVE AS A BACK UP SECONDARY PACKAGER.					
OC RECOMMENDATION	15-MAY-2014			ACCEPTABLE	RHX

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
09/22/2014

ERIC P DUFFY
09/22/2014

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Application:	NDA 21936/000	Action Goal:	
Stamp Date:	16-NOV-2007	District Goal:	26-JUL-2014
Revised Date:	24-SEP-2014		
Applicant:	BOEHRINGER PHARMS 900 RIDGEBURY RD RIDGEFIELD, CT 068770368	Brand Name:	SPIRIVA RESPIMAT
		Estab. Name:	
		Generic Name:	TIOTROPIUM BROMIDE INHALATION SPRAY
Priority:	3S	Product Number; Dosage Form; Ingredient; Strengths	
Org. Code:	570		001; SPRAY; TIOTROPIUM BROMIDE; 2.5UGM

Application Comment: THIS NDA IS THE FIRST INHALATION SPRAY DOSAGE FORM. THE INHALATION SPRAY DELIVERS 2.5 MICROGRAM/ACTUATION OF TIOTROPIUM BROMIDE. THIS IS FOR ORAL INHALATION ONLY. NOTE THAT THE APPLICANT ALSO LISTED TWO ADDITIONAL SITES (b) (4)

THEY ALSO LIST BOEHRINGER INGELHEIM MICROPARTS GMBH, HAUERT 7, 44227 DORMUND, GERMANY AS RESPONSIBLE FOR ALTERNATE TESTING SITE FOR THE RESPIMAT INHALER. THESE TWO SITES WERE NOT ENTERED INTO EES UPON THE RECOMMENDATIONS OF SHAWNTE ADAMS (IN AN EMAIL) STATING THAT THEY WILL NOT BE INSPECTED. THE CONTACT PERSON FOR THE (b) (4) SITE WILL BE REQUESTED AND UPDATED IN EES. (on 20-DEC-2007 by PERIP)

FDA Contacts:	E. NASHED	Prod Qual Reviewer	(HFD-820)	3017961723
	Y. LIU	Product Quality PM		3017961926
	J. LEE	Regulatory Project Mgr		3017963769
	C. BERTHA	Team Leader		3017961646

Overall Recommendation:	ACCEPTABLE	on 11-SEP-2014	by J. WILLIAMS	()	3017964196
	PENDING	on 11-SEP-2014	by EES_PROD		
	ACCEPTABLE	on 11-SEP-2014	by T. SHARP	()	3017963208
	PENDING	on 06-FEB-2013	by EES_PROD		
	PENDING	on 23-DEC-2011	by EES_PROD		
	WITHHOLD	on 22-AUG-2011	by EES_PROD		
	ACCEPTABLE	on 07-MAR-2008	by EES_PROD		

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

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

Establishment Comment: THIS SITE IS RESPONSIBLE FOR ALL ASPECTS OF MANUFACTURING, PACKAGING, AND CONTROL OPERATIONS FOR TIOTROPIUM BROMIDE DRUG SUBSTANCE. IT IS ALSO RESPONSIBLE FOR ALL ASPECTS OF MANUFACTURING, PACKAGING AND CONTROL FOR SPIRIVA RESPIMAT INHALATION SPRAY (on 20-DEC-2007 by PERIP)

Profile: AEROSOL DISPERSED MEDICATION **OAI Status:** NONE
NON-STERILE API BY CHEMICAL SYNTHESIS NONE
DEVICE KIT ASSEMBLER NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					

SUBMITTED TO OC	31-JAN-2008				PERIP
SUBMITTED TO DO	05-FEB-2008	GMP Inspection			ADAMSS
DO RECOMMENDATION	07-MAR-2008			ACCEPTABLE	ADAMSS
OC RECOMMENDATION	07-MAR-2008			ACCEPTABLE	ADAMSS
SUBMITTED TO OC	02-APR-2014				LIUY
SUBMITTED TO DO OAI. PDUFA GOAL DATE: 24-SEP-2014	15-APR-2014	10-Day Letter			SAFAAIJAZIR
UNDER REVIEW	17-APR-2014				PHILPYE
DO RECOMMENDATION	02-JUN-2014			ACCEPTABLE	PHILPYE

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

OC RECOMMENDATION	10-JUN-2014		ACCEPTABLE	IYERS
SUBMITTED TO OC	20-DEC-2007			PERIP
SUBMITTED TO DO	20-DEC-2007	GMP Inspection		ADAMSS
DO RECOMMENDATION	31-JAN-2008		ACCEPTABLE	ADAMSS
OC RECOMMENDATION	31-JAN-2008		ACCEPTABLE	ADAMSS
SUBMITTED TO OC	02-APR-2014			LIUY
SUBMITTED TO DO POAI. PDUFA GOAL DATE: 24-SEP-2014	07-APR-2014	10-Day Letter		SAFAAIJAZIR
DO RECOMMENDATION	11-APR-2014		WITHHOLD	PHILPYE
SL .ED TO DO CSN PROFILE NOW AC.	26-AUG-2014	10-Day Letter		WILLIAMSJU
DO RECOMMENDATION	27-AUG-2014		ACCEPTABLE	MROSE
OC RECOMMENDATION	28-AUG-2014		ACCEPTABLE	WILLIAMSJU
SUBMITTED TO OC	11-SEP-2014			LIUY
OC RECOMMENDATION CDRH/OC RECOMMENDS A POST-APPROVAL INSPECTION WITHIN 6 MONTHS OF PDUFA.	11-SEP-2014		ACCEPTABLE	WILLIAMSJU

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

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

DMF No: AADA:

Responsibilities: FINISHED DOSAGE RELEASE TESTER
 FINISHED DOSAGE STABILITY TESTER

Establishment Comment:

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
<u>Reason</u>					

SUBMITTED TO OC	02-APR-2014				LIUY
SUBMITTED TO DO	03-APR-2014	Product Specific and GMP Inspection			IYERS
DO RECOMMENDATION SHOULD NOT HAVE BEEN PS+GMP - NOT NEW PROFILE	11-APR-2014			ACCEPTABLE	PHILPYE
OC RECOMMENDATION	15-APR-2014			ACCEPTABLE	SAFAAIJAZIR

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: [REDACTED] (b) (4) FEI: [REDACTED] (b) (4)

DMF No: [REDACTED] AADA:

Responsibilities: [REDACTED] (b) (4)
FINISHED DOSAGE STERILITY TESTER

Establishment Comment: [REDACTED] (b) (4) DRUG PRODUCT: (STERILITY TESTING). (on 02-APR-2014 by Y. LIU () 3017961926)

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
<u>Reason</u>					

SUBMITTED TO OC	02-APR-2014				LIUY
SUBMITTED TO DO	03-APR-2014	Product Specific and GMP Inspection			IYERS
DO RECOMMENDATION	11-APR-2014			ACCEPTABLE	MROSE
OC RECOMMENDATION	18-APR-2014			ACCEPTABLE	SAFAAJAZIR

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

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

(b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE LABELER
FINISHED DOSAGE PACKAGER

Establishment Comment:

Profile: AEROSOL DISPERSED MEDICATION OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
<u>Reason</u>					

SUBMITTED TO OC	02-APR-2014				LIUY
SUBMITTED TO DO	04-APR-2014	Product Specific and GMP Inspection			SAFAAIJAZIR
NEW DOSAGE FORM FOR ESTABLISHMENT. PDUFA GOAL DATE:24-SEP-2014					
ASSIGNED INSPECTION TO IB	09-APR-2014	Product Specific and GMP Inspection			DOMBROWSKIR
NEW FORM - PS AND GMP					
DO RECOMMENDATION	12-MAY-2014			ACCEPTABLE	DOMBROWSKIR
EI OF SITE DATED (b) (4) FOUND NAI - FIRM IS SECONDARY PACKAGER IN THIS APPLICATION - FIRM HAD AWARENESS BUT NO ACTIVE INVOLVEMENT TO DATE. STATED TO BE BACK UP SITE TO (b) (4) OPERATION. AGAIN, SECONDARY PACKAGING ONLY.					
SUBMITTED TO DO	13-MAY-2014	10-Day Letter			RHX
PLEASE UPDATE THE MILESTONE					
DO RECOMMENDATION	15-MAY-2014			ACCEPTABLE	DOMBROWSKIR
INSPECTION DATED (b) (4) FOUND ACCEPTABLE - FIRM PERFORMS SECONDARY PACKAGING ONLY. GMP FOR SITE COMPLETED; FIRM HAD KNOWLEDGE OF APPLICATION, BUT IS ONLY EXPECTING TO SERVE AS A BACK UP SECONDARY PACKAGER.					
OC RECOMMENDATION	15-MAY-2014			ACCEPTABLE	RHX

NDA 21-936

**Spiriva[®] Respimat[®] (tiotropium bromide) Inhalation Spray,
2.5* mcg per spray**

* Expressed as tiotropium. Formulated with tiotropium bromide monohydrate (3.124 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

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Chemistry Review Data Sheet

Chemistry Review Sheet

1. NDA 21-936
2. REVIEW NUMBER: 3
3. REVIEW DATE: July 23, 2014
4. REVIEWER: Eugenia M. Nashed, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Submission(s) Reviewed (Chem. Rev. #1 and #2)</u>	<u>Document Date</u>
Original NDA	November 16, 2007
Amendment (BC)	February 11, 2008
Amendment (BC)	February 27, 2008
Amendment (BC)	April 18, 2008
Amendment (BC)	May 21, 2008
Amendment (BC)	June 10, 2008
Amendment (BL)	June 20, 2008
Amendment (BC)	July 01, 2008
Amendment (BC)	July 28, 2008
Amendment (BC)	July 29, 2008
Amendment (BC)	August 05, 2008
Amendment (BC)	August 13, 2008

6. SUBMISSIONS BEING REVIEWED (Chem. Rev. #3):

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendement AC (Resubmission)	March 24, 2014
Amendment (Proprietary name)	April 14, 2014
Amendment (BL)	May 23, 2014
Amendment (BC)	July 21, 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: Spiriva[®] Respimat[®]

Chemistry Review Data Sheet

- 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)

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

10. PHARMACOLOGICAL CATEGORY: Tiotropium is a long-acting anticholinergic with specificity for muscarinic receptor antagonist (LAMA).

11. DOSAGE FORM: Inhalation spray (metered)

12. STRENGTH/POTENCY: 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 (5.0 mcg of tiotropium)

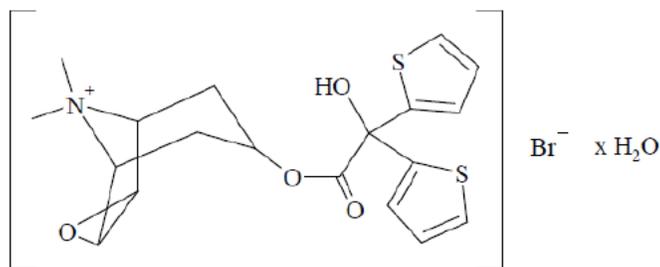
13. ROUTE OF ADMINISTRATION: Oral inhalation

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
 SPOTS product – Form Completed

Not a SPOTS product

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



Tiotropium bromide monohydrate

M.F. : C₁₉H₂₂NO₄S₂Br • H₂O

M.W. : 490.4 (monohydrate);

(b) (4)

USAN name: Tiotropium bromide

IUPAC name: (1 α ,2 β ,4 β ,5 α ,7 β)-7-[(Hydroxydi-2-thienylacetyl)oxy]-9,9-dimethyl-3-oxa-9-azoniatricyclo[3.3.1.0^{2,4}] nonane bromide

Chemistry Review Data Sheet

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)	3	Adequate	10-29-2008 Alan Schroeder, Ph.D. Review includes evaluation of the new synthetic process.	LOA 09-10-2008 The same ds is used in the marketed Spiriva Handi Haler MDI, which is cross-referenced to this NDA.
26,014	3	Boehringer Ingelheim Pharma, GmbH & Co.KG	Container closure for Respimat aqueous solutions (plastic cartridge including plastic cap with integrated sealing ring, and aluminum cylinder)	3	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	3	Adequate	06-17-2014 Erica Englund, Ph.D.	LOA 06-04-2012

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. Review of response to CR letter dated Mar 16, 2013, is pending with PDUFA date Aug 2, 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	4/2/2014	Pending	All sites have AC status (July 23, 2014)
Pharm/Tox	Safety evaluation of controls for impurities, leachables and excipients	N/A	Acceptable Luqi Pei, Ph.D.	Found acceptable during previous review cycle
CDRH OC	Status of device manufacturing site	6/2/2014	Pending Vuniqui/Vicenty, Ph.D.	IR comments proposed for the Applicant. CDER OC and CDRH OC will collaborate to reach a conclusion
CDRH	Engineering aspects of the Respimat device; changes since 2008.	5/6/2014	Pending LeVelle/Lakhani, Ph.D.	IR comment forwarded to Applicant on July 14, 2014
Microbiology	Preservative effectiveness and microbial safety controls during manufacturing and release/stability testing	4/28/2014	Pending Robert Mello, Ph.D.	Review of the updates submitted in resubmission is pending. Acceptable during previous review cycle.
EA	Evaluation of request for Categorical Exclusion	N/A	Acceptable Alan Schroeder, Ph.D.	Previous review cycle
Method Validation	N/A			Consult not planned. Drug substance reviewed under Spiriva HandiHaler. Validation for other analytical methodology addressed during previous review cycle.
Consults regarding drug product name, and labeling were forwarded by DPRP. Reviews by Lissa Owens (6/30/14; Proprietary name), Nichelle Rashid (7/1/14; Proprietary name granted) and Lissa Owens (7/14/14; Labeling review) are filed in DARRTS.				

Executive Summary Section

The Chemistry Review for NDA 21-936

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 provided by the Office of Compliance (OC) and satisfactory recommendation is available from the Microbiology team. The EER for manufacturing and testing facilities is pending and the current status for all sites is listed as acceptable (refer to the EER Summary Report on page 37 of this review). The status of all drug master files (DMFs) supporting this application is Adequate (refer to a summary DMF table on page 6 of this review). In addition, there are two consults pending with CDRH (CDRH/DAGRID/Combination Products and CDRH OC) for the Respimat device and any outstanding comments may have to be addressed.

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:

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 is proposed for treatment of chronic obstructive pulmonary disease (COPD). The drug substance, tiotropium bromide is approved (2004) for treatment of COPD as API in dry powder inhaler Spiriva HandiHaler (NDA 21-395). The Respimat device is approved (2011) as an integral part of Combivent Respimat (ipratropium bromide/albuterol) Inhalation Spray (NDA 21-747) for treatment of COPD. Two additional NDAs from BI with Respimat containing drug products are pending in DPARP: Striverdi Respimat (olodaterol) Inhalation Spray (NDA 203-108, PDUFA 8/2/14), and Stiolto Respimat (tiotropium bromide/olodaterol) Inhalation Spray (NDA 206-756, PDUFA 3/22/15).

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

Executive Summary Section

The drug product formulation is aqueous based, sterile and contained in a sealed cartridge. It contains 0.0226% of tiotropium (b) (4), benzalkonium chloride (preservative), (b) (4) edetate sodium (stabilizer) (b) (4) and hydrochloric acid for pH adjustment (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 2.5 mcg of tiotropium (corresponding to 3.124 mcg of tiotropium bromide monohydrate, which is used in formulation) (b) (4). A dose is comprised of two actuations, i.e., 5.0 mcg of tiotropium delivered in 22.2 µL volume, (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 hygroscopic crystalline powder (b) (4)

Tiotropium bromide is a quaternary ammonium salt related to atropine. It is present in the approved drug product: Spiriva HandiHaler (tiotropium bromide) Inhalation Powder, NDA 21-395 (Approved 2004).

Note:

The Spiriva® Respimat® (tiotropium bromide) Inhalation Spray product containing 1.25 mcg of tiotropium per spray is not proposed for marketing under this NDA. However, a substantial amount of CMC data was submitted to this NDA for 1.25 mcg/spray formulation. The 1.25 mcg/spray formulation was used during clinical development and it is briefly discussed further down in this review. While the provided data for 1.25 mcg/spray drug product indicate comparable quality, performance and stability of this formulation to the proposed for marketing 2.5 mcg/spray drug product the extent of review and provided data is not sufficient to warrant the approval of 1.25 mcg/spray drug product for marketing.

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 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.

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 aqua-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

Executive Summary Section

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 9 batches of the 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, satisfactory recommendation from the Microbiology review team as well as from the CDRH review teams evaluating the Respimat device.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemistry Reviewer: Eugenia Nashed, Ph.D.

Acting CMC Lead: Craig Bertha, Ph.D.

Division Director/Acting Branch Chief: Eric Duffy, Ph.D.

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

34 Pages have been Withheld in Full as B4 (CCI/TS)
Immediately Following this Page

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/s/

EUGENIA M NASHED
07/25/2014

CRAIG M BERTHA
07/25/2014
Signing for Dr. Eric Duffy
I concur

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

- I. Review Cover Sheet
- II. Application Detail
- III. Filing Checklist
- IV. Manufacturing Summary
- V. Overall Conclusions and Recommendations

I. Review Cover Sheet

1. OMPQ Reviewer: Linda Ng, Ph.D.
2. NDA/BLA Number: NDA 21-936
Submission Date: March 24, 2014
21st C. Review Goal Date: July 26, 2014
PDUFA Goal Date: September 24, 2014

3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	Spiriva Respimat ®
Established or Non-Proprietary Name (USAN) and strength:	TIOTROPIUM BROMIDE INHALATION SPRAY
Dosage Form:	Inhaler Spray

4. SUBMISSION PROPERTIES:

Review Priority :	Standard; Re-submission
Applicant Name:	Boehringer Ingelheim International GmbH
Responsible Organization (OND Division):	DPARP

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review
For Pre-Marking Applications

II. Application Detail

1. INDICATION: TREATMENT OF BRONCHOSPASM ASSOCIATED WITH CHONIC OBSTRUCTIVE PULMONARY DISEASE(CODP), INCLUDING CHRONIC BRONCHITIS AND EMPHYSEMA
2. ROUTE OF ADMINISTRATION: Inhalation
3. STRENGTH/POTENCY: 0.023% (2.5 µg per actuation in ^{(b) (4)} cartridge)
^{(b) (4)}
- 4.
5. Rx/OTC DISPENSED: Rx OTC
6. ELECTRONIC SUBMISSION (yes/no)? Yes
7. PRIORITY CONSIDERATIONS: No

	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	x			
10.	Other (e.g., expedited for an unlisted reason)		x		

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review
For Pre-Marking Applications

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)	X		
	1. Are all sites registered or have FEI #?			
	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.

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review
For Pre-Marking Applications

B. DRUG SUBSTANCE (DS) / DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
16.	Have any Comparability Protocols been requested?		X	No statement made. None could be located

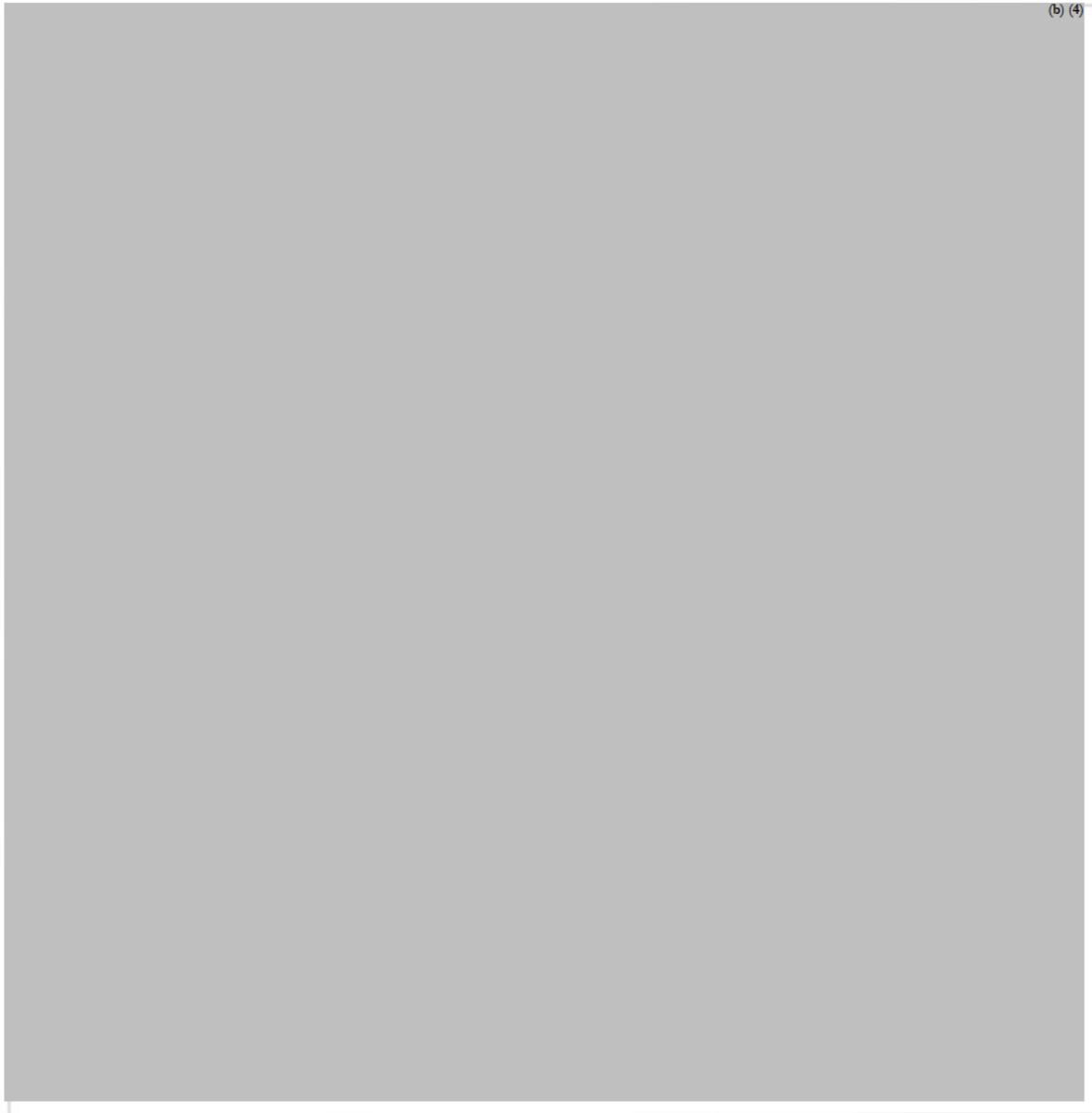
IMA CONCLUSION				
	Parameter	Yes	No	Comment
17.	Does this application fit one of the EES Product Specific Categories?		X	
18.	Have EERs been cross referenced against the 356h and product specific profile for accuracy and completion? Have all EERs been updated with final PAI recommendation?	X		Not all EER been updated with final PAI recommendations
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?			
<input type="checkbox"/>	RTRT Proposal <input type="checkbox"/>	PAT <input type="checkbox"/>	Drug/Device Combo X <input type="checkbox"/>
PET <input type="checkbox"/>	Design Space <input type="checkbox"/>	Continuous Mfg <input type="checkbox"/>	Naturally derived API <input type="checkbox"/>
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	
<p>Include process flow chart/diagram (see eCTD Section 2.3.S.1)</p>				
2. Drug Product				
	Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, unusual control strategy)?	X		Sterile Inhaler spray
<p>Include process flow chart/diagram (see eCTD Section 2.3.P.1)</p>				

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review
For Pre-Marking Applications



OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review
For Pre-Marking Applications

(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.**

Not likely.

- 4. Drug Product Facility Inspectional History that could impact the manufacturing of this product**

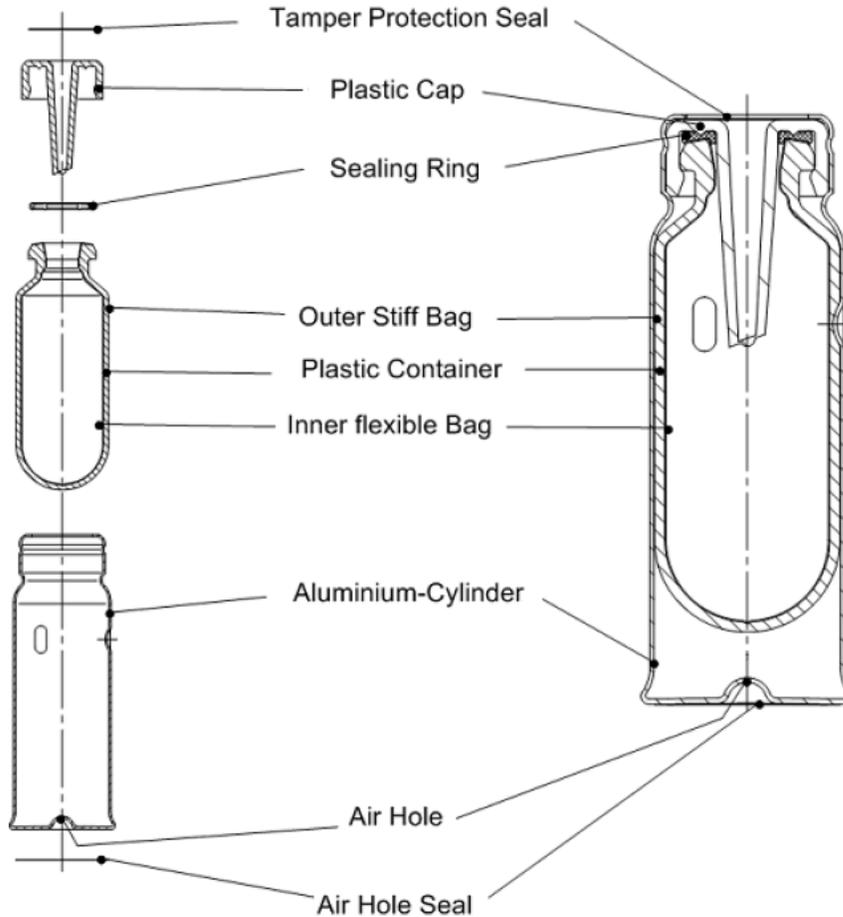
Inspection in April 2014 at Boehringer Ingelheim, Germany was a follow up to a Warning Letter. The results were VAI recommendation with 483 issued. According to

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review
For Pre-Marking Applications

FACTS, the DO recommends AC. OMPQ has yet to evaluate and reach a final decision.

Additional information not covered above

Drawing of container closure (exploded and assembled)



OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review
For Pre-Marking Applications

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

NDA:	21936 SPIRIVA RESPIMAT											
Sponsor:	BOEHRINGER INGELHEIM PHARMACEUTICALS INC											
Indication:	Treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis & emphysema											
PDUFA:	9/24/2014 under Priority Review											
Responsible Organization:	CDER/ODEII/DPARP											
EERS Submitted By:	LIU, YOUNG: CDER/ONDQA											
Chart Generated On:	5/2/2014											
Overall OC Recommendation: PENDING entered into EES on 2/6/2013 6:03:27 PM												
Reevaluation date:												
Establishment Name	EER Creation Date	FEI Num	District Short	Country Code	Responsibilities	Profile Code	Firm Profiles - Current Status	Inspection History, Dates, Classifications	Facts Assignment Id	Most Recent Milestone	Most Recent EER Compliance Status	Comment
(b) (4)										ASSIGNED INSPECTION TO B	PN	
BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG	1/31/2008	3002806556	EEU	DEU	Manufacturing, Analytical testing (all release & stability tests except sterility).	ADM	(b) (4)	Inspection of (b) (4) was found AC by DO		UNDER REVIEW	PN	OAI Alert
(b) (4)										SUBMITTED TO DO	PN	
BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG	12/10/2007	3002806556	EEU	DEU	manufacturing, packaging, labeling, release and stability testing (including	CSN	(b) (4)	Inspection of (b) (4) was found AC by DO		DO RECOMMENDATION	PN	OAI Alert
(b) (4)										OC RECOMMENDATION	AC	
(b) (4)										OC RECOMMENDATION	AC	
(b) (4)										OC RECOMMENDATION	AC	

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review
For Pre-Marking Applications

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. Not likely. The drug product facility has been inspected April 2014.
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
05/23/2014

MAHESH R RAMANADHAM
05/27/2014

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application : NDA 21936/000 Sponsor: BOEHRINGER PHARMS
Org Code : 570 900 RIDGEBURY RD
Priority : 3S RIDGEFIELD, CT 06877

Stamp Date : 16-NOV-2007 Brand Name : SPIRIVA RESPIMAT
PDUFA Date : 16-SEP-2008 Estab. Name:
Action Goal : Generic Name: TIOTROPIUM BROMIDE INHALATION
District Goal: 18-JUL-2008 SPRAY
Dosage Form: (SPRAY)
Strength : 2.5 MICROGRAMS/SPRAY

FDA Contacts: M. RAGGIO Project Manager 301-796-2109
P. PERI Review Chemist 301-796-1730
A. AL HAKIM Team Leader 301-796-1323

Overall Recommendation: ACCEPTABLE on 07-MAR-2008 by S. ADAMS (HFD-325) 301-796-3193

Establishment : CFN : 9610492 FEI : 3002806556
BOEHRINGER INGELHEIM PHARMA KG
D-55216 IINGELHEIM AM RHEIN
INGELHEIM, , GM

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 : ADM OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 07-MAR-08
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION
Profile : CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 31-JAN-08
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

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

DMF No: AADA:

Responsibilities: (b) (4)
FINISHED DOSAGE OTHER TESTER

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 31-JAN-08
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

NDA 21-936

Spiriva[®] Respimat[®] (tiotropium bromide inhalation spray)

Boehringer Ingelheim Pharmaceuticals, Inc.

Chemistry Review #2

Date: August 15, 2008

Recommendation: Approval

**Alan C. Schroeder, Ph.D.
ONDQA/Division I/Branch II**

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Chemistry Review Data Sheet

1. NDA 21-936
2. REVIEW #: 2
3. REVIEW DATE: August 15, 2008
4. REVIEWER: Alan C. Schroeder, Ph.D.

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original NDA	16-Nov-2007

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment (BC)	11-Feb-2008
Amendment (BC)	27-Feb-2008
Amendment (BC)	18-Apr-2008
Amendment (BC)	21-May-2008
Amendment (BC)	10-Jun-2008
Amendment (BL)	20-Jun-2008
Amendment (BC)	23-Jun-2008
Amendment (BC)	01-Jul-2008
Amendment (BC)	28-Jul-2008
Amendment (BC)	28-Jul-2008
Amendment (BC)	29-Jul-2008
Amendment (BC)	05-Aug-2008
Amendment (BC)	13-Aug-2008

Executive Summary Section

7. NAME & ADDRESS OF APPLICANT:

Name: Boehringer Ingelheim Pharmaceuticals, Inc.
Address: 900 Ridgebury Rd., P.O. Box 368
Ridgefield, CT 06877
Jeffrey R. Snyder
Representative: Executive Director
Drug Regulatory Affairs
Telephone: 203-778-7727

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Spiriva Respimat
- b) Non-Proprietary Name (USAN): tiotropium bromide inhalation spray
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: anticholinergic with specificity for muscarinic receptors

11. DOSAGE FORM: spray, metered (inhalation spray)

12. STRENGTH/POTENCY: 2.5 mcg per inhalation (as the tiotropium (b) (4))

13. ROUTE OF ADMINISTRATION: respiratory (inhalation)

14. Rx/OTC DISPENSED: Rx OTC

15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):

Executive Summary Section

____ SPOTS product – Form Completed

 x Not a SPOTS product

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

INN: Tiotropium Bromide

US Adopted Name (USAN): Tiotropium bromide

Chemical Name (IUPAC): (1 α ,2 β ,4 β ,5 α ,7 β)-7-[(Hydroxydi-2-thienylacetyl)oxy]-9,9-dimethyl-3-oxa-9-azoniatricyclo[3.3.1.0^{2,4}] nonane bromide

Chemical Abstracts Name: 3-Oxa-9-azoniatricyclo[3.3.1.0^{2,4}] nonane, 7-[(hydroxydi-2-thienylacetyl)oxy]-9,9-dimethyl-, bromide, monohydrate (1 α ,2 β ,4 β ,5 α ,7 β)-.

The CAS number is 411207-31-3.

Laboratory code: BA 679 BR

Molecular Formula: C₁₉H₂₂NO₄S₂Br * H₂O

Molecular Weight: 490.4 (monohydrate); (b) (4)

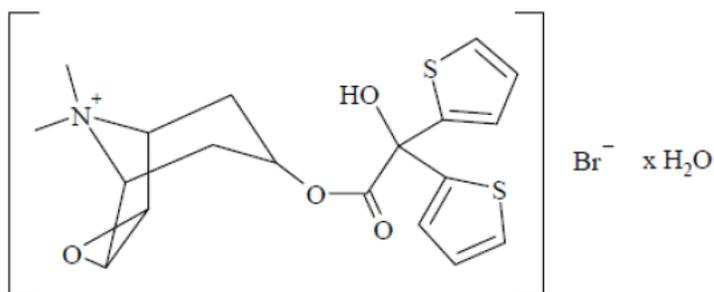


Figure 1: Chemical structure of tiotropium bromide monohydrate

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
18135	II	Boehringer Ingelheim Pharma	tiotropium bromide monohydrate	1	Adequate	13 Jun 2008	\
17322	III	Boehringer Ingelheim microParts (BImP)	Respimat inhaler (device)	1	Adequate	24 July 2008	
17403	III	BImP	plastic cap with	1	Adequate	10 Jul 2008	DMF (b) (4) is

Executive Summary Section

			integrated sealing ring (for cartridge)				a supporting DMF (see below). Extractables/leachables data are provided in the NDA to support the safety of the plastic cap and (b) (4)
(b) (4)	III		(b) (4)	1	Adequate	20 Jun 2008	
	III		3	Adequate	31-Jul-2006 (A. Shaw)	Reviewed for Ciclesonide Nasal Spray (N22-004) – note that N21-936 contains results of extractables/testing of the component	
	III		1	Adequate	28 May 2007		
	III		1	Adequate	23 June 2008		
	III		1	Adequate	24 July 2008	supports DMF 17322	
	III		1	Adequate	21 May 2008		

Executive Summary Section

(b) (4)	III	cartridge)	(b) (4)	1	Adequate	23 May 2008	(b) (4)
	III		4			see below.	
	III		7			LOA (dated 2/26/2004) is provided in DMF (b) (4). See comments in this NDA chemistry review #2	
							Review not needed since this (b) (4) has been discontinued.

¹ Action codes for DMF Table:

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

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

Note that the letters of authorization may be found in Module 1 (volume B1.1) for DMFs 18135, 17322, 17403, (b) (4). [NOTE: DMFs (b) (4) do not have LOAs in this section – see Table 17 on pg. approx. 95 of this review where they are mentioned by the applicant for materials for Respimat device components, but without LOAs.]

*LOAs for these DMFs in the above table are in DMF 17322; the applicant has also listed the DMF numbers.

Note that there is no Drug Master File cited for the manufacturer of the (b) (4) (b) (4). The level of risk for this component appears to be relatively low here since the drug formulation is aqueous, and in view of the following information. The applicant studied the (b) (4) extractables and leachables (b) (4)

Executive Summary Section

(b) (4), and no leachables were found for this component above the LOQ; additionally, the applicant states that the (b) (4) component complies with USP <88> requirements.

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	65,127	Spiriva Respimat
IND	46,687	Tiotropium Bromide Inhalation Powder

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	consult not required - decision is based on the applicant's stability analyses and the quality of the stability data.		
EES	Acceptable	March 7, 2008	S. Adams (HFD-325)
Pharm/Tox	Acceptable (safety evaluation of impurities, extractables and leachables, and excipients)	May 6, 2008	Luqi Pei, Ph.D. (DPAP)
Biopharm	not required		
LNC (ONDQA)	“inhalation spray” as the dosage form in the labeling, found to be adequate by Dr. Rik Lostritto	Based on informal discussion	
Methods Validation	Methods verification by FDA Laboratories is not required. The methods have been validated and problems with the methods were not reported. Note that the equipment used for laser diffraction & Andersen Cascade Impactor methods contains some custom made components that would be very difficult to replicate by FDA laboratories.		
OPDRA			
EA	Request for categorical exclusion is acceptable.		See evaluation in this review
Microbiology	AE	July 2, 2008	Anastasia G. Lolas
	AP	August 14, 2008	Anastasia G. Lolas

Executive Summary Section

CDER OSE		(DPAP consult)	
DDMAC		(DPAP consult)	
Radiopharmaceutical	N.A.		
CDRH (device)	“No specific concerns or issues were identified regarding the manufacturing and quality control for the device.” Human factors studies and usability studies are recommended, and these have previously been addressed in the NDA.	June 1, 2008 memo (included in DMF 17322 review dated July 24, 2008}	Sugato De (comments incorporated into Alan Schroeder’s DMF review)

The Chemistry Review for NDA 21-936

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application may be approved from a CMC standpoint.

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

The applicant has agreed:

to revisit the extractable specifications for the RespiMat (device) components after 1 year (estimated 10 inhaler batches);

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

to reevaluate the drug product specifications (acceptance criteria) as more release and stability data pertaining to commercial batches is obtained from at least 10 commercial batches for the U.S. Market. BI agrees to collect data from both Aerodynamic Particle Size Distribution methods, employing the Andersen Cascade Impactor and the Laser Diffraction methods in addition to collecting data pertaining to the remainder of the specifications.

to inform the FDA about each “quality relevant change” of the analytical procedure for aerodynamic particle size distribution (APSD-LD) including the instrument, instrumental attachments, software and procedure in a supplemental application consistent with the requirements of 21 CFR 314.70; to evaluate each change “by a risk analysis as part of BI’s internal changes control procedure to verify the influence of the change on the analytical determination;” to confirm “all quality relevant changes by revalidation and depending on the change, supported by comparative data.”

to incorporate into the applicable documents (e.g., the specification documents) the drug product specification and method changes agreed to during the course of the NDA review. No other changes besides those listed by BI will be incorporated.

There are additional labeling comments in the section of this review pertaining to the June 20, 2008 amendment for future labeling discussions with the applicant. This includes comments (b) (4) provided by the applicant in the original NDA will need to be revised.

Executive Summary Section

II. Summary of Chemistry Assessments**A. Description of the Drug Product(s) and Drug Substance(s)**

The NDA for Spiriva Respimat (tiotropium bromide inhalation spray) is apparently the first NDA for this new dosage form, an inhalation spray. The Respimat device is a “cylindrical shaped plastic inhalation device with a gray colored body and a clear base” and the inhaler has a green colored cap. The cartridge is “an aluminum cylinder with a green colored seal on the cap.” The drug product must not be subject to freezing conditions, since they will damage the cartridge. One actuation of Spiriva Respimat *delivers from the mouthpiece* 2.5 mcg of tiotropium (b) (4) (equal to 3.1 mcg of tiotropium bromide monohydrate); the delivered volume per inhalation is (b) (4). One dose is two inhalations (therefore the delivered dose is 5 mcg tiotropium (b) (4) equal to 6.2 mcg of tiotropium bromide monohydrate, in 22.2 mcL of solution).

(b) (4)
(b) (4)
(b) (4)
(b) (4) The minimum fill of the drug product cartridge (reservoir) is indicated to be 4.0 mL. This represents an overfill of (b) (4). This considerable amount of overfill is not available to the patient since the device locks after approximately 30 doses (60 actuations) are dispensed. The Respimat device contains an actuation counter. The drug product produces an aerosol by mechanical means; there is no propellant. The drug product must be primed before its first use, and reprimed if not used for specified intervals; this is described in the draft labeling.

The drug formulation is an aqueous solution, packaged in a two component plastic container (reservoir) inside an aluminum can (cylinder; this combination is designated as the “cartridge.”). The solution formulation contains, in addition to the drug substance, water for injection, (b) (4) hydrochloric acid, benzalkonium chloride, and EDTA (edetate disodium). (b) (4)

Executive Summary Section

(b) (4)

(b) (4) The drug substance is in the monohydrate form. Solid state characteristics are not critical for the drug product since the formulation is a solution. (b) (4)

(b) (4) Tiotropium bromide is also used in the marketed product, Spiriva Handihaler, a dry powder inhaler.

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

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

The drug product is primed before first use by actuating it until a spray is visible, and then actuating it three more times. If the product is not used for more than (b) (4) days, it is reprimed by releasing one actuation. If the product is not used for more than 21 days, it is reprimed by following the initial priming instructions.

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

A single dose of drug product is two inhalations ex-mouthpiece (a total of 5 µg of tiotropium (b) (4)). This drug is for the long-term, once-daily, maintenance treatment of patients with bronchospasm associated with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema.

The proposed expiration dating period is (b) (4) months when stored at 25°C, with excursions permitted between 15°C and 30°C as explained in the US Pharmacopeia. This is supported by primary stability data (through (b) (4) months) and supporting stability data

Executive Summary Section

(through 36 months). The maximum in-use life of the product (after the cartridge is inserted into the Respimat device) is 3 months, and this is supported by in-use stability data.

It is possible to switch cartridges in the Respimat device, however, this is not permitted by the labeling, and the drug product locks after 30 doses, therefore this puts an absolute limit on a patient trying to reuse the device with another cartridge.

C. Basis for Approvability or Not-Approval Recommendation

Manufacturing and control of the drug substance is referenced to the applicant's type II DMF, which was previously reviewed for a marketed drug product, and this DMF for the drug substance is acceptable.

CDRH has provided a consult review of the Respimat device. This review is included in a review of the device DMF #17322. The manufacturing and controls of the device were found to be adequate by CDRH. Since the drug product (cartridge) is manufactured to be sterile, the microbiology group in OPS has provided two consult reviews (recommendation: approval) of the microbiological aspects of the drug product and the manufacturing process of the filled cartridge. The review pharmacologist has provided a consult review of the drug product for a safety review of drug related impurities, degradation products, leachables, foreign particulates, the benzalkonium chloride and disodium edetate excipients, and the USP <87> and <88> testing of critical inhaler components. These were found to be adequate.

There have been multiple versions of the Respimat inhaler during the development of this tiotropium bromide inhalation spray drug product. (b) (4)

Respimat A4 was used for Phase III clinical supplies (and the supporting stability batches) and Respimat A5 (the proposed commercial inhaler) was used for the primary stability batches. Respimat A4 was also used for most of the drug product characterization studies. (b) (4)

Respimat A5 is said to differ from Respimat A4 "only in that it includes a new design of the dose indicator, a locking mechanism and a product specific cap color." The applicant has conducted a small scale *in vitro* study (b) (4) on three batches each of A4 and A5 Respimat inhalers. Results are similar, (b) (4)

Summary APSD data from Respimat A4 and Respimat A5 drug product appear to be similar, and there is a larger amount of data available from the primary and supporting stability studies to compare the A4 and A5 Respimat products. The supportive NDA stability batches used the A4 device and the primary NDA stability batches used the A5 device. These stability data sets were both found to support the proposed expiry period for the drug product.

Additional information requested in Information Request letters has been found to be adequate in this review.

Executive Summary Section

Overall, this drug product appears to be reasonably rugged and consistent in its performance, and the data are within the proposed acceptance criteria at release and in the primary NDA stability studies. Over the use life of the product, from beginning to end, there is [REDACTED] (b) (4) [REDACTED] in delivered dose (based on stability data), but this is fairly consistent and within the acceptance criteria. The main changes on stability are a slight decrease in assay and an increase in degradation products. Performance is consistent on stability.

It is noted that the Division of Pulmonary and Allergy Products has decided that labeling will not be discussed further with the applicant during this review cycle, therefore additional labeling comments included in this review will be sent to the applicant in the next review cycle.

III. Administrative

A. Reviewer's Signature

See electronic signature block at end of review in DFS.

B. Endorsement Block

Alan C. Schroeder, Ph.D./Date: 15 Aug 2008
Ali Al-Hakim, Ph.D./
ProjectManager Miranda Raggio/

C. CC Block

52 Pages have been Withheld in Full as B4 (CCI/TS)
Immediately Following this Page

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

/s/

Alan Schroeder
8/15/2008 11:13:19 AM
CHEMIST

Ali Al-Hakim
8/15/2008 11:17:57 AM
CHEMIST

NDA 21-936

Spiriva[®] Respimat[®] (tiotropium bromide inhalation spray)

Boehringer Ingelheim Pharmaceuticals, Inc.

Chemistry Review #1

Date: April 18, 2008

Recommendation: AE

**Alan C. Schroeder, Ph.D.
ONDQA/Division I/Branch II**

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Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. NDA 21-936
2. REVIEW #: 1
3. REVIEW DATE: April 18, 2008
4. REVIEWER: Alan C. Schroeder, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous DocumentsDocument Date

N.A.

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) ReviewedDocument Date

Original NDA

16-Nov-2007

7. NAME & ADDRESS OF APPLICANT:

Name: Boehringer Ingelheim Pharmaceuticals, Inc.
Address: 900 Ridgebury Rd., P.O. Box 368
Ridgefield, CT 06877
Jeffrey R. Snyder
Representative: Executive Director
Drug Regulatory Affairs
Telephone: 203-778-7727

8. DRUG PRODUCT NAME/CODE/TYPE:

Chemistry Review Data Sheet

- a) Proprietary Name: Spiriva Respimat
b) Non-Proprietary Name (USAN): tiotropium bromide inhalation spray
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: anticholinergic with specificity for muscarinic receptors

11. DOSAGE FORM: spray, metered

12. STRENGTH/POTENCY: 2.5 mcg per inhalation

(b) (4)

13. ROUTE OF ADMINISTRATION: respiratory (inhalation)

14. Rx/OTC DISPENSED: Rx OTC

15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):

SPOTS product – Form Completed

Not a SPOTS product

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

INN: Tiotropium Bromide

US Adopted Name (USAN): Tiotropium bromide

Chemical Name (IUPAC): (1 α ,2 β ,4 β ,5 α ,7 β)-7-[(Hydroxydi-2-thienylacetyl)oxy]-9,9-dimethyl-3-oxa-9-azoniatricyclo[3.3.1.0^{2,4}] nonane bromide

Chemical Abstracts Name: 3-Oxa-9-azoniatricyclo[3.3.1.0^{2,4}] nonane, 7-[(hydroxydi-2-thienylacetyl)oxy]-9,9-dimethyl-, bromide, monohydrate (1 α ,2 β ,4 β ,5 α ,7 β)-.

Chemistry Review Data Sheet

The CAS number is 411207-31-3.

Laboratory code: BA 679 BR

Molecular Formula: C₁₉H₂₂NO₄S₂Br * H₂O

Molecular Weight: 490.4 (monohydrate); (b) (4)

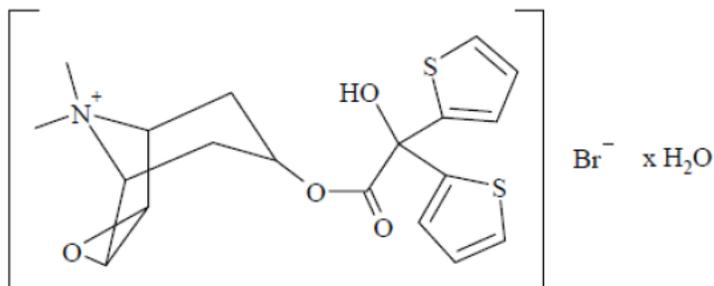


Figure 1: Chemical structure of tiotropium bromide monohydrate

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
18135	II	Boehringer Ingelheim Pharma	tiotropium bromide monohydrate	3	Adequate	17 Dec 2007 (Dr. Edwin Jao)	Reviewed for BI's NDA 21-395 (Spiriva HandiHaler)
17322	III	Boehringer Ingelheim microParts (BImP)	Respimat inhaler (device)			pending	A copy was provided along with a consult review request to CDRH
17403	III	BImP	plastic cap with integrated sealing ring			pending	
(b) (4)	III	(b) (4)	(b) (4)			pending	
(b) (4)	III	(b) (4)	(b) (4)			pending	
(b) (4)	III	(b) (4)	(b) (4)			pending	
(b) (4)	III	(b) (4)	(b) (4)			pending	

Chemistry Review Data Sheet

(b) (4)	III					pending	
	III					pending	
	III					pending	This (b) (4) replaces previously used (b) (4) see below.
	III					pending	??location of LOA?
	III			7			Review not needed - (b) (4)
							(b) (4) This (b) (4) has been discontinued.

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

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

Note that the letters of authorization may be found in Module 1 (volume B1.1) for DMFs 18135, 17322, 17403, (b) (4). [NOTE: DMFs (b) (4) do not have LOAs in this section – see Table 17 on pg. approx. 95 of this review where they are mentioned by the applicant for materials for RespiMat device components, but without LOAs.]

Chemistry Review Data Sheet

*LOAs for these DMFs in the above table are in DMF 17322; the applicant has listed the DMF numbers.

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	65,127	Spiriva Respimat
IND	46,687	Tiotropium Bromide Inhalation Powder

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	consult not required - decision is based on the applicant's stability analyses and the quality of the stability data.		
EES	Acceptable	March 7, 2008	S. Adams (HFD-325)
Pharm/Tox	pending (request submitted ca. 2/5/08)		
Biopharm	not required		
LNC	"inhalation spray" as the dosage form in the labeling, found to be adequate by Dr. Rik Lostritto		
Methods Validation	The decision on MV is stayed pending additional internal discussion and applicant's response to IR letter		
OPDRA			
EA	Request for categorical exclusion is acceptable.		See evaluation in this review
Microbiology	pending (submitted ca. 2/5/08)		
CDER OSE	pending	(DPAP consult)	
DDMAC	pending	(DPAP consult)	
Radiopharmaceutical	N.A.		
CDRH (device)	pending (request submitted 2-15-08)		

Executive Summary Section

The Chemistry Review for NDA 21-936

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is approvable, pending adequate resolution of the comments sent (and to be sent) to the applicant, pending adequate supporting DMFs to be reviewed separately, pending adequate consult reviews and pending a determination by the Office of Compliance that the manufacturing and testing facilities are adequate. It is intended that there will be an additional CMC review within the initial review cycle. Structured product labeling will be reviewed in the next review, and well as the responses to the items above.

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

II. Summary of Chemistry Assessments

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

The NDA for Spiriva Respimat (tiotropium bromide inhalation spray) is the first NDA for this new dosage form, an inhalation spray. The Respimat device is a “cylindrical shaped plastic inhalation device with a gray colored body and a clear base” and the inhaler has a green colored cap. The cartridge is “an aluminum cylinder with a green colored seal on the cap.” The drug product must not be subject to freezing conditions, since they will damage the cartridge. One actuation of Spiriva Respimat *delivers from the mouthpiece* 2.5 mcg of tiotropium (b) (4) (equal to 3.1 mcg of tiotropium bromide monohydrate); the delivered volume per inhalation is (b) (4). One dose is two inhalations (therefore the delivered dose is 5 mcg tiotropium (b) (4) equal to 6.2 mcg of tiotropium bromide monohydrate, in (b) (4) solution). (b) (4)

(b) (4) The minimum fill of the drug product cartridge (reservoir) is indicated to be 4.0 mL. This represents an overfill (b) (4) (b) (4) (for the minimum fill of 4.0 mL). This considerable amount of overfill is not available to the patient since the device locks after 30 doses (60 actuations) are dispensed. The Respimat device contains an actuation counter. The drug product produces an aerosol by mechanical means; there is no propellant. The drug product must be primed before its first use, and reprimed if not used for specified intervals; this is described in the draft labeling.

Executive Summary Section

The drug formulation is an aqueous solution, packaged in a two component plastic reservoir inside an aluminum can (cylinder; this combination is designated as the “cartridge.”).

(b) (4)

(b) (4)

The patient inserts the canister into the Respimat device, which meters the formulation and produces the aerosol spray. The solution formulation contains, in addition to the drug substance, water for injection, (b) (4) hydrochloric acid, benzalkonium chloride, and EDTA (edetate disodium).

The drug substance, tiotropium bromide, is a quaternary ammonium salt related to atropine.

(b) (4)

(b) (4)

(b) (4). The drug substance is in the monohydrate form. Solid state characteristics are not critical for the drug product since the formulation is a solution.

(b) (4)

(b) (4) Tiotropium bromide is also used in the marketed product, Spiriva Handihaler, a dry powder inhaler.

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

A single dose of drug product is two inhalations ex-mouthpiece (a total of 5 µg of tiotropium (b) (4)). This drug is for the long-term, once-daily, maintenance treatment of

Executive Summary Section

patients with bronchospasm associated with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema.

The drug product is initially primed by actuating it until a spray is visible, and then it is actuated three more times. If the product is not used for more than (b) (4) days, it is primed by releasing one actuation. If it has not been used for more than 21 days, it is reprimed by following the original priming procedure. The patient uses the product by holding it upright, and turning the clear base in the direction of the red arrows until it clicks (one half turn). The green cap is opened, the patient puts his or her lips around the mouthpiece, and actuates it by pressing the dose release button while breathing in slowly. The mouthpiece of the inhaler and the metal piece inside the mouthpiece are to be cleaned weekly by wiping with a damp cloth or tissue.

The proposed expiration dating period is (b) (4) months when stored at 25°C, with excursions permitted between 15°C and 30°C as explained in the US Pharmacopeia. This is supported by primary stability data (through (b) (4) months) and supporting stability data (through 36 months). The maximum in-use life of the product (after the cartridge is inserted into the Respimat device) is 3 months, and this is supported by in-use stability data.

It is possible to switch cartridges in the Respimat device, however, this is not permitted by the labeling, and the drug product locks after 30 doses, therefore this puts an absolute limit on a patient trying to reuse the device with another cartridge.

C. Basis for Approvability or Not-Approval Recommendation

Manufacturing and control of the drug substance is referenced to the applicant's type II DMF, which was previously reviewed for a marketed drug product, and this DMF for the drug substance is acceptable.

CDRH has been asked to provide a consult review of the Respimat device. Since the drug product (cartridge) is manufactured to be sterile, the microbiology group in OPS has been asked to provide a consult review of the microbiological aspects of the drug product and the manufacturing process of the filled cartridge. The review pharmacologist has been asked to provide a consult review of the drug product for a safety review of drug related impurities, degradation products, leachables, foreign particulates, the benzalkonium chloride and disodium edetate excipients, and the USP <87> and <88> testing of critical inhaler components.

There have been multiple versions of the Respimat inhaler during the development of this tiotropium bromide inhalation spray drug product. The applicant states that the basic operating principles of the device (for dosing and aerosolization) were not changed over the development process. (b) (4) Respimat A4 was used for Phase III clinical supplies (and the supporting stability batches) and Respimat A5 (the proposed commercial inhaler) was used for the primary stability batches. Respimat A4 was also used for most of the drug product characterization studies. (b) (4)

Executive Summary Section

(b) (4) Respimat A5 is said to differ from Respimat A4 “only in that it includes a new design of the dose indicator, a locking mechanism and a product specific cap color.” The applicant has conducted a small scale *in vitro* study on multiple batches of A4 and A5 Respimat inhalers (b) (4) three batches of A4, three batches of A5 Respimat inhalers). Results are similar. (b) (4)

Summary APSD data from Respimat A4 and Respimat A5 drug product appear to be similar, and there is a larger amount of data available from the primary and supporting stability studies to compare the A4 and A5 Respimat products.

The applicant has been asked (or will be asked) in Information Request letters, to provide the following information: data pertaining to residual (b) (4) in the drug product (b) (4); information to address our concern that the patient may lose labeled actuations due to necessary priming actuations, since the drug product locks after 60 actuations; additional information to enable assessment of the aerodynamic particle size distribution methods; the reasons for using the large overfill in the drug product; a reference to where CMC information may be found in the IND and NDA for the 0.045% comparator product (5 µg per spray) used in clinical studies; information on any controls on the amount of force required to insert and properly seat the cartridge in the device, and to comment on the potential difficulty of the procedure of cartridge insertion for certain patients, especially elderly patients. In addition, a number of other clarifications and information have been requested from the applicant.

Overall, this drug product appears to be reasonably rugged and consistent in its performance, and the data are within the proposed acceptance criteria at release and in the primary NDA stability studies. Over the use life of the product, from beginning to end, there is a (b) (4) in delivered dose (based on stability data), but this is fairly consistent and within the acceptance criteria. The main changes on stability are a slight decrease in assay and an increase in degradation products. Performance is consistent on stability. The levels of degradation products permitted by the acceptance criteria are being reviewed by the pharmacology/toxicology reviewer, Dr. Luqi Pei.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Alan C. Schroeder, Ph.D./Date: Same date as draft review
Ali Al-Hakim, Ph.D./Date
ProjectManager MRaggio/

C. CC Block

145 Pages have been Withheld in Full as B4 (CCI/TS) Immediately Following this Page

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

/s/

Alan Schroeder
5/20/2008 11:09:27 AM
CHEMIST

Ali Al-Hakim
5/20/2008 04:32:22 PM
CHEMIST

OND Division of Pulmonary and Allergy Products

NDA: 21-936

Applicant: Boehringer Ingelheim

Stamp Date: 16-Nov-2007

PDUFA Date: 16-Sep-2008

Proposed Proprietary Name: Spiriva Respimat

Established Name: Tiotropium bromide

Dosage form and strength: Inhalation Spray (first in house), 2.5 µg tiotropium base per actuation *ex mouthpiece*. One dose (5 µg) consists of two actuations. Spray weight of two actuations is 22.1 mg (b) (4)

Established name/Dosage form nomenclature was forwarded to Dr. Rik Lostritto for his evaluation.

Route of Administration: Oral Inhalation

Indications: long-term, once-daily, maintenance treatment of patients with bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.

Proposed Dose: The dose regimen is 1 dose per day. The labeled number of doses per cartridge is 30 doses (60 metered actuations).

PAL: Prasad Peri, Ph.D. Branch 2/DPA I/ONDQA

Fileability recommendation: Acceptable for filing

Review team recommendation: Primary reviewer: Alan Schroeder, Ph.D.

Time goals:

Initial Quality Assessment (Filing Date): by 28-Jan-2008 (Found acceptable for filing)

Chemistry filing memo in DFS: by 28-Jan-2007

Filing decision "Day 60": **18-Jan-2008** (30 days!)

74 Day letter Due: 1-Feb-2008 (tentative; to be set by Clinical Division)

Chemistry Review (DR/IR) letter: by 18-Apr-2008 ! (tentative)

Mid-cycle meeting "Month 5": 18-Apr-2008 (set by Clinical Division)

Advisory Committee Meeting: N/A

Full Labeling Meeting: ~ 11-Jul-2008

Wrap-up: 18-Jul-2008

Labeling Tcon: ~25-Jul-2008

Final Chemistry Review "Month 8" in DFS: by 16-Jul-2008

PDUFA: 16-Sep-2008

Related Documents

INDs pertaining to this are: 43,704,

(b) (4)

USAN/INN	Tiotropium Bromide	
Chemical Name IUPAC	(1 α ,2 β ,4 β ,5 α ,7 β)-7-[(Hydroxydi-2-thienylacetyl)oxy]-9,9-dimethyl-3-oxa-9-azoniatricyclo[3.3.1.0] nonane bromide	
Chem Abstracts	3-Oxa-9-azoniatricyclo[3.3.1.0] nonane, 7-[(hydroxydi-2-thienylacetyl)oxy]-9,9-dimethyl-,bromide, monohydrate (1 α ,2 β ,4 β ,5 α ,7 β)-.	
CAS #	411207-31-3	
Molecular Formula	C ₁₉ H ₂₂ NO ₄ S ₂ Br * H ₂ O	
Molecular weight	490.4 (monohydrate);	(b) (4)

Structure	
CONSULTS/ CMC RELATED REVIEWS	COMMENT
Clinical Pharm (BA/BE) - Dissolution	Not applicable
CDRH	Device to be consulted
EA	To be assessed by Primary Reviewer
EES	EES for all 4 sites listed were sent out on Nov. 19, 2007
DMETS/DDMAC	Consensus is pending. Dosage form is an Inhalation Spray. Dr. Rik Lostritto consulted for his evaluation of the established name and dosage form
Methods Validation	To be sent when appropriate
Microbiology	To be sent for sterility validation and the evaluation of microbial limits.
Pharm/Tox	Consult to be sent for evaluation of safety of the proposed levels of impurities and degradants. Leachables of the mouthpiece needs to be evaluated.
Biometrics	To be decided by the reviewer

Summary:

- This is a standard 10 month NDA paper NDA in CTD format with electronic labeling provided in SPL format. There is a Quality Overall Summary (83 pages). This NDA is filed as a 505(b) 1 application.
- This is classified as a new dosage form as per MaPP 7500.

Drug Substance

- The drug substance is referenced to a Boehringer Ingelheim Pharma GmbH & Co.KG's Type II Drug Master File (DMF #18135) that is also referenced for the approved NDA for Spiriva® Handihaler®. This DMF was reviewed in support of a Dry Powder Inhaler formulation (Spiriva® Handihaler®).
- The applicant (BIPI) holds the DMF and claims the DMF lists two grades of Tiotropium bromide. One grade is for the DPI formulation and one is for a solution formulation. "The inhalation solution quality differs from the inhalation powder quality only in the inclusion of a microbiological specification and in the absence of a particle size specification. For Spiriva® Respimat®, the inhalation solution quality is relevant".
- DMF was last reviewed by Dr. Edwin Jao for the DPI formulation on 12/17/07 and found adequate. Since the drug product is a solution, the PSD for the drug product is not essential in this drug product. Hence it is not necessary for an extensive review of the DMF in support of this NDA. Drug substance specifications are reproduced below. Batch analyses data are provided for 11 batches in the NDA (module 3). The microbial testing for the solution formulation is relevant in the drug product as well.

Drug Product

- The product Spiriva® Respimat® consists of a sterile aqueous inhalation solution of tiotropium bromide monohydrate in a cartridge and a Respimat® inhaler. The principle of the Respimat® inhaler is to meter a small volume of the inhalation solution and to press it through a nozzle with two fine outlets. (b) (4) resulting in the spray which is inhaled by the patient. The cartridge with the inhalation solution and the Respimat® inhaler are supplied as two entities in one package. Prior to first use, the patient inserts the cartridge into the inhaler.

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Prasad Peri, Ph.D., Division of Pre-Marketing Assessment 1, Branch 2

- The composition of the drug product is shown on the next page. The basic principle of the device is provided in the development pharmaceuticals in detail. In short, when the device is actuated, two jets of solution collide against each other to create a spray. This spray is a slow moving spray compared to that of a MDI. The metered volume is provided by a pressure differential generated within the capillary tube by the patient turning the device 180 degrees.
- The device has a sliding dose indicator that moves from the green zone to a red zone as the device is used. The dose indicator is combined with a locking mechanism that locks the Respimat® inhaler to prevent further use when the labeled number of 30 doses has been reached. After locking it is no longer possible to turn the lower part of the inhaler, rendering the Respimat® inhaler unusable.
- The cartridge (reservoir) that contains the drug solution consists of two elements: a primary packaging which is a double walled plastic container which is closed with a plastic cap with integrated sealing ring and a secondary packaging: an aluminum cylinder (with an air hole seal) and a tamper protection seal. The patient inserts the cartridge into the Respimat® inhaler, the inhaler capillary tube pierces the tamper-protection foil and the piercing point of the cap shaft, thus immersing in the solution in the cartridge. At the same time, a pin in the inhaler lower part pierces the air hole seal in the cylinder bottom. (b) (4)

- The cartridge should not be frozen, as the formation of ice damages the polymer bags. This is also stated on the label. The cartridge contains a minimum fill of 4 ml. As the declared number of 30 doses (b) (4)

Overfills are common to multi-dose inhalation products. The Respimat® overfill is required for proper container functionality. The locking mechanism of the Respimat® inhaler guarantees that the overfill cannot be extracted from the cartridge. Therefore, in contrast to pMDIs, the overfill is, not accessible to the patient.

Table 5: Composition of Spiriva® Respimat®

Name of Ingredient	Function	Reference to Standards	Per dose ¹ (Label Claim) (mg)	Percentage Formula (g/100ml)	Per cartridge ⁴ (mg)
Tiotropium ²			0.005		(b) (4)
corresponds to Tiotropium bromide monohydrate	Drug substance	In house standard			(b) (4)
Benzalkonium chloride ³	Preservative	NF			(b) (4)
Edetate Disodium	Stabilizer	USP			(b) (4)
(b) (4) Hydrochloric acid		(b) (4) NF			(b) (4)
Water for injection		USP			(b) (4)
Total weight			(b) (4)	100.0	(b) (4)

Table 6: Metered and delivered volume of Spiriva® Respimat®

Metered and delivered volume of Spiriva® Respimat®	Volume per dose
Metered volume (<i>ex valve</i>)	(b) (4)
Delivered volume (<i>ex mouthpiece</i>)	22.1 µl

Figure 3 shows the Respimat® inhaler with the cartridge inserted and the aerosol generated; the cartridge alone is shown in Figure 4, the inhalation is shown in Figure 5:

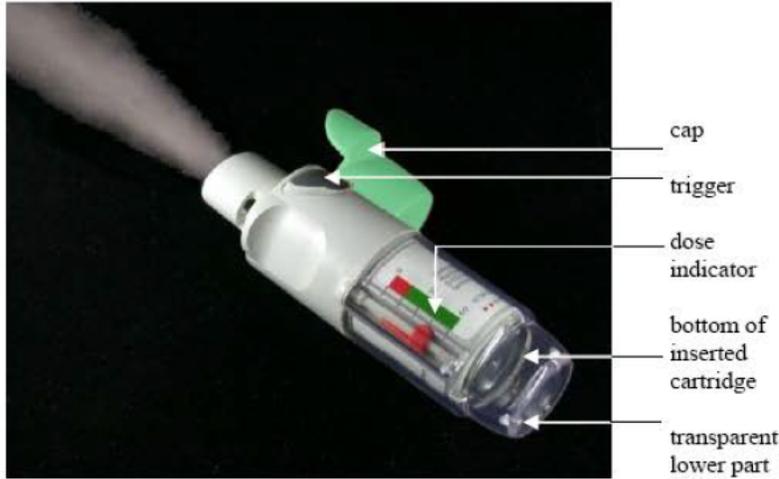


Figure 3: Spiriva® Respimat® inhaler with cartridge inserted and aerosol generated



Figure 4: Cartridge (shown without labeling text)



Figure 5: Patient inhaling Spiriva® Respimat®

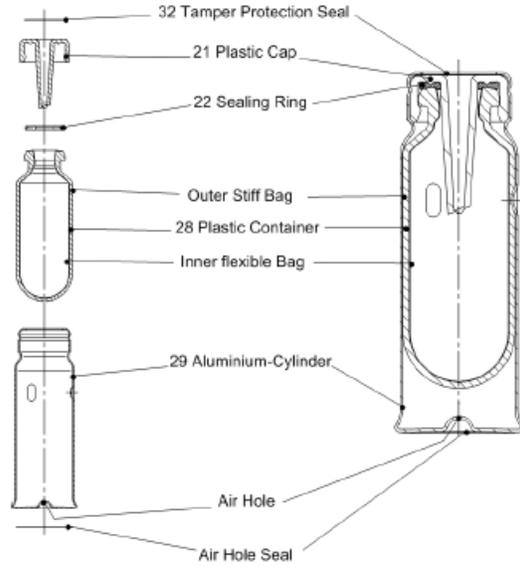
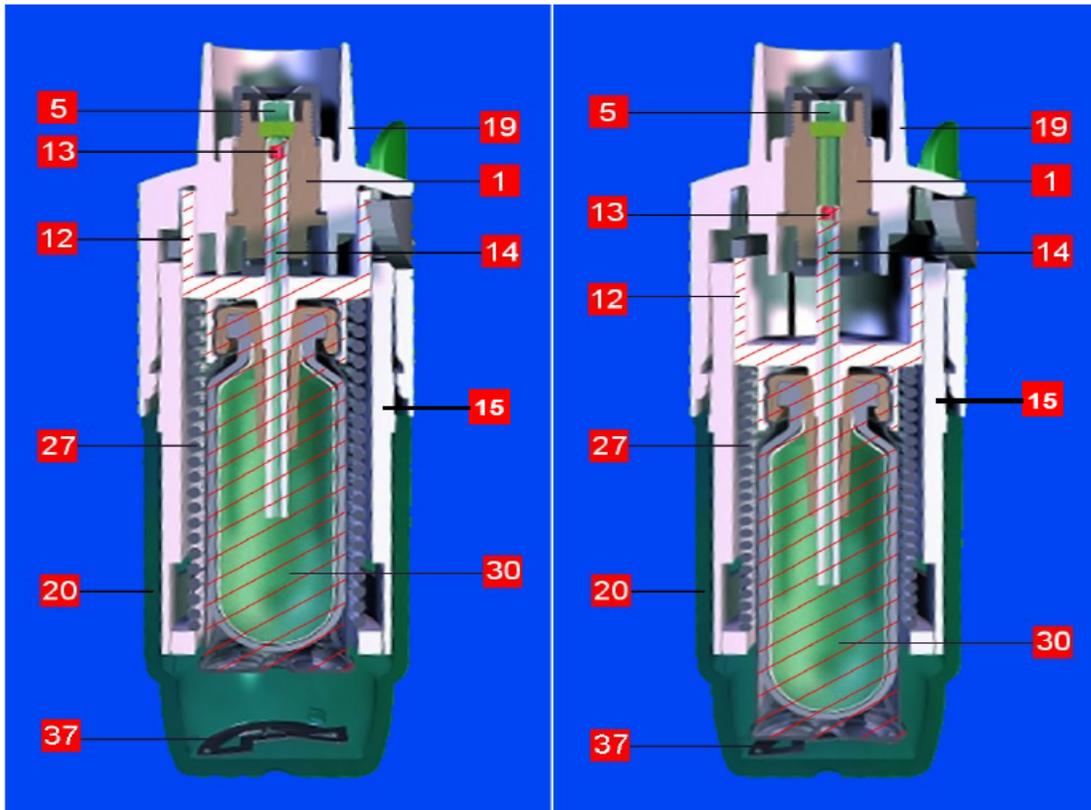


Figure 6: Schematic drawing of the cartridge

ATTACHMENT 6: CROSS SECTION SHOWING THE FUNCTION OF THE RESPIMAT® INHALER



After actuation
 Capillary in upper position

Prior to actuation
 Capillary in lower position

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

No.	Component	Function / Description	Material / type	Material supplier / DMF
1	Central Tube			(b) (4)
4	Uniblock Seal			
5	Uniblock			
6	Prefilter Holder			
7	Prefilter			
8	O-Ring 4x1			
9	O-Ring 1.4 x 1.1			
13	Valve Body			
14	Capillary tube			
19	Case Upper Part			

- **Container closure system.**

See figures above.

CRITICAL ISSUES

- **Pharmaceutical development**

Although the drug product is processed sterile, the formulation contains benzalkonium chloride as the preservative. The pH of the solution (b) (4) is necessary for the stability of the drug product solution. All excipients used meet pharmacopial grade and stability of the solution and its compatibility with the cartridge and Respimat inhaler has been used. Drug product characterization studies for the following parameters are reported in the NDA.

- A) Priming / Repriming in Various Orientations / Effect of Resting Time
- B) Temperature Cycling
- C) Cleaning Instructions
- D) Device Robustness
- E) Effect of Dosing Orientation
- F) Tail Off Characteristics
- G) Plume geometry
- H) Preservative Effectiveness and Sterility Maintenance
- I) Stability of Primary (Unprotected) Package
- J) Characterization of Individual Actuations

- **Dose Dumping**

Not applicable.

- **Microbial Testing**

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

- **In-process controls**

In-process controls include pH-control, control of bioburden, integrity (b) (4), fill mass, integrity of the filled reservoirs, and measurement of the dimensions of the crimped cartridge.

- **Critical Quality Attributes/ Process parameters**

The applicant discusses Delivered Dose, PSD, Microbiological status, Functionality during use, Extractables and Leachables in the critical quality attributes of the drug product.

The sponsor states that the longer the time between two doses, the lower the delivered mass and dose (b) (4). The applicant believes that in the Respimat® inhaler, (b) (4) causes the effect. For the first labeled dose, both modes of actuations deliver the same doses; for the last labeled dose, the “sequential mode” gives results that are (b) (4). Both results are independent of the age of the inhaler and consistent over inhaler batches. The applicant plans to use sequential use mode while release testing and hence has labeled when tested as sequentially tested.

The particle size distribution of Spiriva® Respimat® is set by the geometry of the nozzle (“uniblock”) and by the force of the spring that expels the solution. The two jets of solution are designed to be (nozzle angle) 90 degrees to each other. The APSD is characterized by maximum deposition in the stages 3-5 of the ACI. By laser, the sum of APSD diameter (b) (4)

The inhalation solution in an unopened cartridge is sterile. (b) (4) manufacturing has been chosen and has been assured by validation. Once the cartridge is inserted into the Respimat inhaler, the solution has a permanent connection to the non sterile environment via capillary tube, central tube, and uniblock and may face microbiological contamination. The sponsor counteracts the possible microbiological contamination during use by preservation of the inhalation solution. Preservative effectiveness complies with USP requirements. The sponsor investigated the microbiological status of Spiriva® Respimat® under realistic conditions of use. These need to be evaluated by the microbiological staff. Inhalers with inserted cartridges were actuated under laboratory conditions for exposure times of one and three months to simulate the in-use period; then, the solution remaining in the cartridge was sampled: 4 out of 54 cartridges showed 1 cfu/ml; all other cartridges showed no contamination. Cartridges used by patients in the phase III clinical trials were investigated. They showed negligible microbiological burden (b) (4)

Functionality and in use studies indicated that the devices are fairly robust. Results from returns program indicated that the delivered dose and APSD were comparable to the release results.

- **Overage in the formulation.**

No overages in the formulation are proposed. An over fill (b) (4) is used during the manufacture of the cartridge. The sponsor claims unlike a MDI the over-fill is not available for the patient since the device locks out after 30 doses (60 actuations).

- **Excipients from Animal Origin.**

None

- **OVI in the drug Product**

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

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

Cartridge design: Phase III supplies had used (b) (4). Due to a discontinuation of supply, the commercial product will use (b) (4). For phase III product, the plastic cap (b) (4). This was optimized for the commercial product in that the plastic container also is (b) (4). The changes did not influence the properties of the product, as indicated by unchanged batch release and stability data. For a tabular presentation, please refer to Attachment 3, page 68 of the QOS

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

- the Respimat® version A4 – it has been used in the Phase III clinical studies (Study nos. 205.249, 205.250, 205.251, 205.252, 205.254, and 205.255), which demonstrate the safety and efficacy and serve as basis for the dose selection (see CTD Module 2.5: Clinical Overview), and in supportive stability studies
- the Respimat® version A5, which is intended for the commercial product; it has been used in primary stability studies

The key development step from Respimat® A4 to Respimat® A5 was the inclusion of a locking mechanism to lock the Respimat® A5 after 30 doses. Further changes between the two versions are merely cosmetic (e.g., change in cap color). Neither uniblock nor the cartridge system nor the composition of the solution was changed. The locking mechanism does not interfere with the dosing and nebulization before locking. Table 7 demonstrates the equivalence of the two versions of the device by comparing *in vitro* performance data of product batches.

Table 7: Comparison of *in vitro* performance of the Phase III supplies and market configuration

	Clinical supply for Phase III study	Product in market configuration
Respimat® type used	Respimat® A4	Respimat® A5
Batch no. solution / Respimat® inhaler	e.g.: 202820 / WE 01070189	e.g.: 405441 / 3U0024
Target delivered dose [µg]	5	5
Delivered dose [µg] *	(b) (4)	
Aerodynamic particle size distribution by ACI [% of target dose in Group 1 / 2 / 3]		
Aerodynamic particle size distribution by Laser [% of particles in Group 1 / 2 / 3]		

* Delivered dose values for Batch 202820 / WE 01070189 were determined according to the draft FDA Guidance “Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products”; for batch 405441 / 3U0024, they are given as start (S) and end (E) values of the spray content uniformity test.

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

Both drug substance and drug products are manufactured at the BI site in Germany. An alternate site (b) (4) is responsible for microbiological testing of the drug substance and drug product. Both sites are pending EES status.

- **Safety of imprinting inks.**

Not applicable

- **Dissolution of the drug product.**

Not applicable

- **Degradation products:**

A scheme for the degradation pathway is provided below. The proposed levels of degradants (see Drug Product Specifications) are claimed to be qualified. These need to be assessed by pharmtox reviewers. A consult needs to be sent to the pharmacologist to evaluate the levels of proposed degradants in the drug product. Note that these levels are due to the fact that the formulation is a solution (b) (4). The sponsor claims that the proposed specification limits for the individual degradation products do not raise any toxicological concerns (cf. Non-Clinical Overview, chapter “Impurities, degradation products and packaging materials”).



Figure 11: Tiotropium degradation scheme

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

The applicant states that **extractable** profiles of the critical inhaler parts have been investigated with three solvents of different polarities. The key extractables found with organic solvents were consistent between batches and are (see also Table 18, page 63):

(b) (4)

BI indicates that aqueous extraction yielded no extractables from any components except traces of (b) (4) from the case upper part. These (b) (4) were also found during investigations on the **leachables** profile of the case upper part (mouthpiece). The low amounts assure that only negligible quantities of substances can migrate (b) (4) into human saliva within the seconds of contact with the patient's mouth.

The sponsor indicates that all plastic materials of the critical Respimat® inhaler components comply with 21CFR regulations or, for the case upper part material, have been shown to comply with USP <87> and <88>. A risk assessment showed that there is no (b) (4) concern. The levels of leachables have been assessed as non-critical in the Non-Clinical Overview, chapter "Impurities, degradation products and packaging materials". **Note an Extractable Leachable correlation needs to be established at least for the components in contact with Saliva and the formulation.**

The sponsor proposes not to test for leachables. The applicant claims that this is justified by the established controls of all primary container closure components for extractables and by the design of the formulation as an aqueous system. It is supported by the extremely low leachable levels found during long-term stability studies (b) (4) and by the results of extractable studies with water as solvent. Leachables levels are below (b) (4) at all time points. They do not show a trend over time. For details, see Section 2.3.P.7.2.2, page 57 of QOS.

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

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

- **Shelf life of the drug product (proposed (b) (4)).**

The company applies for a shelf-life of (b) (4) at room temperature (25°C; excursions permitted to 15–30°C). This includes a maximum in-use period of 3 months. There is the label statement that the product should be protected from freezing.

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

None proposed

- **Drug Product Stability**

The applicant has shown that the drug product is quite stable for (b) (4) months. Real time data for 3 batches using the A4 device (36 months of 25/60 and 6 months 40/75) and 3 batches using the A5 device (24 months of 25/60 and 6 months 40/75). The shelf life is limited by the degradation of the drug substance in the formulation. As per the sponsor, no influence of time was observed for: Content of benzalkonium chloride, Content of disodium edetate, pH, Color and clarity of the solution, Particulate matter, Sterility, Preservative effectiveness test, Spray content uniformity and Number of doses, Pump delivery, Aerodynamic particle size distribution by Andersen Cascade Impactor, and Particle size distribution by laser diffraction

- **Analytical Methods**

Of significance, note that an alternate method for APSD determination by laser diffraction is provided. The sponsor claims that there is adequate correlation between the laser diffraction droplet size distribution method and the APSD determined by Cascade Impactor. **This needs to be further evaluated. While testing of APSD, the applicant has combined the mass of drug product in the Adaptor-mouthpiece, Standard Induction Port (SIP), and Stages 0-2 of the Andersen Cascade Impactor in Group 1. As a result there is a substantial amount of drug deposited in Group 1 as per the acceptance criteria. A rationale for this is not provided in the QOS.**

- **Comparability Protocol**

None proposed.

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

This is a combination drug product. A formal consult for CDRH will be sent to review this device.

- **In-use stability period**

The in-use stability of the product with the cartridge inserted into the Respimat® inhaler has been investigated on samples of the 1st stability set. The chemical stability – it was investigated on freshly manufactured and on aged batches; degradation pattern and rate are identical to the ones in the unopened cartridge (report no. H011187) – as well as microbiological quality and performance stability (report no. H008974) are assured for a period of up to 3 months. This is the claimed use period.

Table 2: Specification for tiotropium bromide monohydrate

Test	Acceptance Criteria	Test method
Appearance	White to yellowish white powder	Visual Test
Identity-IR	The frequency and relative intensity of the absorption peaks in the sample spectrum correspond to those in the reference spectrum.	IR spectroscopy
Identity-Melting point	(b) (4)	DSC
Identity-Bromide	Complies	Precipitation
Color of the Solution (1% aqueous solution)	Not more intensely coloured than reference solution Y6	Limit Test
Clarity of the Solution (1% aqueous solution)	Not more opalescent than the reference suspension I	Limit Test
Chromatographic purity	(b) (4)	HPLC
	Every other unspecified impurity	
	Total of all impurities	
	(b) (4)	TLC
Heavy Metals	(b) (4)	Limit test with (b) (4)
Residual Solvents	(b) (4)	GC
Water	(b) (4)	(b) (4)
Sulphated Ash	(b) (4)	Weighing
Assay (calculated with reference to the anhydrous substance)	(b) (4)	HPLC
	(b) (4)	Titration with (b) (4)
Microbiological Purity	Total viable aerobic count (b) (4)	Microbiological determination in accordance with USP
	(b) (4)	

The table below shows the stability batches for the drug substance used in the manufacture of the drug product.

1 = 270343 (used in Phase II clinical trial supplies of Spiriva® Respimat®)	7 = 1008384 (used in stability studies)
2 = 1000959 (used in Phase III clinical trial supplies of Spiriva® Respimat®)	8 = 1012784 (used in stability studies)
3 = 1001134 (used in Phase III clinical trial supplies of Spiriva® Respimat®)	9 = 1013637 (used in stability studies)
4 = 1001276 (used in stability studies)	10 = 1013708 (used in stability studies)
5 = 1008456 (used in stability studies)	11 = 1013623 (used in stability studies)
6 = 1008322 (used in stability studies)	---

Table 12: Proposed Regulatory Specifications for Spiriva® Respimat®

Test Parameter	Acceptance Criteria	Test Method	Analytical procedure no.
Appearance	<u>Cartridge</u> : Liquid, filled into (b) (4) cartridges crimped in aluminium cylinders for Respimat® with a turquoise colored tamper protection seal. No defects affecting the quality of the product should be discernible. <u>Device</u> : Respimat® Inhaler with turquoise cap.	Visual	021622 000001
Color of solution	Not more intensely coloured than reference solution B7	quantitative color determination	020188
Clarity of solution	Not more opalescent than reference suspension I	quantitative turbidity measurement	020189
pH	(b) (4)	potentiometric	020190
Volume of contents (b) (4)	:4.00 ml per cartridge (tested only at release)	Gravimetric	020191
Loss of mass	(b) (4) mg per cartridge (tested only during stability)	gravimetric, relative to initial weight	020198
Identification	<u>TLC</u> : The Rf value of the active ingredient obtained with the sample solution corresponds to that obtained with the standard solution. <u>HPLC</u> : The retention time obtained with the sample solution corresponds to that obtained with the standard solution. <u>Bromide</u> : The mV-value obtained with the sample solution is in the same range as the mV-value obtained with the standard solution.	TLC, HPLC, potentiometric	020199 (TLC) 020539 (HPLC) 020200 (potentiometric)

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Prasad Peri, Ph.D., Division of Pre-Marketing Assessment 1, Branch 2

Test Parameter	Acceptance Criteria	Test Method	Analytical procedure no.
Impurities: (b) (4)	(b) (4)	HPLC, HPLC-MS (b) (4) (b) (4)	020192 (HPLC) 020538 (HPLC-MS)
Any unidentified degradation product Sum of all degradation products			
Assay	(b) (4), Tiotropium /100 ml (b) (4), of target)	HPLC	020201
Content of benz- alkonium chloride	(b) (4) 100 ml	HPLC	020202
Content of disodium edetate	(b) (4) / 100 ml	complexometric titration	020203
Particulate matter (b) (4)	Not more than (b) (4) Not more than (b) (4) particles per Not more than (b) (4) cartridge (tested only at release)	Light obscuration according to USP <788>	009921
Sterility	meets the requirements of the test for sterility	USP <71>	012613
Spray content uniformity (SCU)	Mean (beginning and end): (b) (4), of target dose (TD) Individual doses: at least 18 of 20: (b) (4) of TD and 20 of 20: (b) (4) of TD Second tier as given in FDA's Guidance "Nasal Spray and Inhalation Solution, Sus- pension, and Spray Drug Products"	Sampling apparatus, USP <601>, flow (b) (4), HPLC determination	020206
Pump delivery	Mean: (b) (4) of target value (b) (4), 20 individual values: (b) (4) of target value	Gravimetric	020207

Test Parameter	Acceptance Criteria	Test Method	Analytical procedure no.
Aerodynamic parti- cle size distribution			
<u>Regulatory method:</u> Andersen Cascade Impactor	<u>Group 1</u> (b) (4) (b) (4) Mouthpiece- Adapter, SIP, Stage 0 – 2): (b) (4) <u>Group 2</u> (b) (4) ((b) (4) µm: Stage 3 – 4): (b) (4) <u>Group 3</u> (b) (4) (b) (4) Stage 5 - 7, (b) (4): (b) (4) All data in % of target dose of 5 µg	USP <601>, Ander- sen cascade impac- tor, controlled environ- ment, individual stage assay (HPLC)	020208
<u>Alternative method:</u> Laser diffraction	<u>Group 1</u> (b) (4) <u>Group 2</u> (b) (4) <u>Group 3</u> (b) (4) All data in % of particles	Laser diffraction, controlled environ- ment	020209
Number of doses	not less than 30 doses	Calculation from SCU results	020221

Set	Cartridge and Respimat® inhaler batch nos.	inhaler version	composition	batch size (kg)	use of batch	stability data reported (months) ^a	Stability report nos.	Remark
1 st	202820 / WE01070189	A4	identical	(b) (4)	phase III clinical supply (study 205.254); stability batch	0, 3, 6, 9, 12, 18, 24, 36	solution parameters: H011185 (cartridge)	---
	202820/ WE01080199				phase III clinical supply (studies 205.249, 205.250, 205.255)	0, 3, 6, 9, 12, 18, 24, 36		---
	202948 / WE01070187				phase III clinical supply (studies 205.251, 205.252); stability batch	0, 3, 6, 9, 12, 18, 24, 36		Executed batch record provided
	204543 / WE01070188				Stability batch	0, 3, 6, 9, 12, 18, 24, 36		---
3 rd	405441 / 3U0024	A5	identical	(b) (4)	Primary stability batch	0, 3, 6, 9, 12, 18, 24	H012912	---
	405766 / 3U0025				Primary stability batch	0, 3, 6, 9, 12, 18, 24		---
	405792 / 3U0026				Primary stability batch	0, 3, 6, 9, 12, 18, 24		Executed batch record provided

* : Long-term storage (25°C / 60%RH): 3 and 6 months data also after accelerated storage (40°C / 75%RH)

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The following table summarizes all proposed commercial manufacturing, packaging and control sites for drug substance and drug product. All sites are ready for inspection.

Establishment	Registration Number (FEI)	Activity
Tiotropium Bromide Monohydrate Drug Substance		
Boehringer Ingelheim Pharma GmbH & Co. KG Binger Straße 173 55216 Ingelheim am Rhein Germany Contact: Dr. Michael Pfeiffer Quality Operations Department Boehringer Ingelheim Pharma GmbH & Co. KG Telephone: +49 6132-77-7013 Facsimile: +49 6132-77-8950	3002806556	All aspects of manufacturing, packaging, and control operations, for tiotropium bromide monohydrate drug substance.
(b) (4)		
Spiriva® Respimat® Inhalation Spray Drug Product		
Boehringer Ingelheim Pharma GmbH & Co. KG Binger Straße 173 55216 Ingelheim am Rhein Germany Contact: Dr. Michael Pfeiffer Quality Operations Department Boehringer Ingelheim Pharma GmbH & Co. KG Telephone: +49 6132-77-7013 Facsimile: +49 6132-77-8950	3002806556	All aspects of manufacturing, packaging, and control operations, for Spiriva® Respimat® Inhalation Spray.
(b) (4)		

DMF no.	Type	DMF Holder	Content	Comments
18135	II	BIP and KG	Tiotropium Bromide	Minor review
Component DMFs:				
17322	III	Boehringer Ingelheim microParts (BImP)	Respimat® inhaler	To be reviewed
17403	III	BImP	Plastic cap with integrated sealing ring	To be reviewed
(b) (4)	III	(b) (4)	(b) (4)	To be reviewed

ONDQA PAL's Initial Quality Assessment
Prasad Peri, Ph.D., Division of Pre-Marketing Assessment 1, Branch 2

		Plastic material DMFs:				
(b) (4)	III				(b) (4)	To be reviewed
	III				To be reviewed	
	III				To be reviewed	
	III				To be reviewed	
	III				To be reviewed	
	III				To be reviewed	
	III				To be reviewed	

Set	Cartridge and Respimat® inhaler batch nos.	inhaler version	composition	batch size (kg)	use of batch	(b) (4)	stability data reported (months) [*]	Stability report nos.	Remark	
1 st	202820 / WE01070189	A4	identical	(b) (4)	phase III clinical supply (study 205.254); stability batch		0, 3, 6, 9, 12, 18, 24, 36	solution parameters: H011185	---	
	202820 / WE01080199				phase III clinical supply (studies 205.249, 205.250, 205.255)		0, 3, 6, 9, 12, 18, 24, 36 (cartridge)		---	
	202948 / WE01070187				phase III clinical supply (studies 205.251, 205.252); stability batch		0, 3, 6, 9, 12, 18, 24, 36		performance parameters: H011186	Executed batch record provided
	204543 / WE01070188				Stability batch		0, 3, 6, 9, 12, 18, 24, 36		---	
3 rd	405441 / 3U0024	A5	identical	(b) (4)	Primary stability batch		0, 3, 6, 9, 12, 18, 24	H012912	---	
	405766 / 3U0025				Primary stability batch		0, 3, 6, 9, 12, 18, 24		---	
	405792 / 3U0026				Primary stability batch		0, 3, 6, 9, 12, 18, 24		Executed batch record provided	

* Long-term storage (25°C / 60%RH), 3 and 6 months data also after accelerated storage (40°C / 75%RH)

CHEMISTRY NDA FILEABILITY CHECKLIST

IS THE CMC SECTION OF APPLICATION FILEABLE? Yes

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

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

Draft CMC Comments for the Applicant

1. Provide a rationale for combining the Adaptor-mouthpiece, Standard Induction Port (SIP) and Stages 0-2 of the Andersen Cascade Impactor in Group 1 during the measurement of the APSD for the drug product. As a result we note that there is a substantial amount of drug deposited in Group 1.
2. Provide a sample of the Drug Product.

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

/s/

Prasad Peri
2/1/2008 01:58:23 PM
CHEMIST

Ali Al-Hakim
2/1/2008 03:37:13 PM
CHEMIST