

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203108Orig1s000

CHEMISTRY REVIEW(S)

NDA 204 677

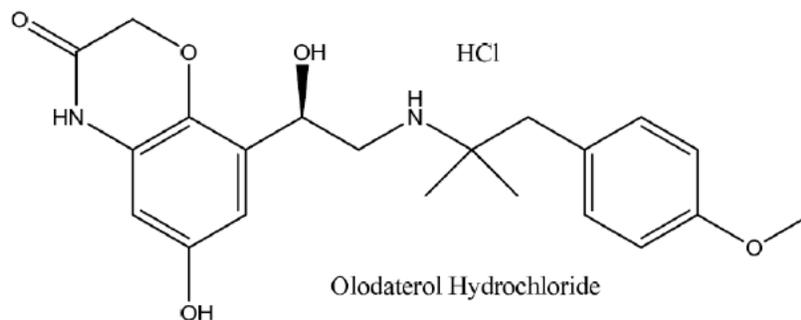
**Striverdi Respimat
(olodaterol) Inhalation Spray**

Boehringer Ingelheim Pharmaceuticals, Inc.

**Chemistry, Manufacturing, and Controls
Division Director's Summary Basis of Action**

Applicant: Boehringer Ingelheim Pharmaceuticals, Inc.

900 Ridgebury Road
P.O. Box 368
Ridgefield, Ct 06877



Strength/Potency:

Each spray delivers 2.7 mcg of olodaterol HCl equivalent to 2.5 mcg olodaterol. Dose is 2 inhalations once per day

EER Status:

The Office of Compliance issued an overall recommendation of ACCEPTABLE for the application on 16-JUN-2014

Drug Substance:

The drug substance olodaterol hydrochloride is a white to off-white (b) (4)

(b) (4) Stability data support a (b) (4) retest period.

Drug Substance: Satisfactory

Drug Product:

This NDA from Boehringer Ingelheim for Striverdi® Respimat® (olodaterol inhalation spray) is the third NDA submitted for this new type of dosage form. The drug product consists of an aluminum/plastic cartridge containing a sterile aqueous formulation that is inserted in a Respimat® delivery device. The Respimat® delivery device is the same one proposed to be used for all three inhalation spray applications that have been submitted by the applicant. Once inserted by the patient, the unit must be primed prior to first use. Patients need to be cautious and not subject the cartridges to freezing conditions, which would damage the cartridge. The current proposed once-daily dose is two actuations or inhalations from the inhaler, which delivers a total volume of formulation for both actuations of 22.1 mL, containing 5.4 mcg of olodaterol hydrochloride, which is equivalent to 5.0 mcg of olodaterol. The device delivers 60 actuations after priming for a total of 30 doses and it locks to prevent further use once these doses are delivered and counter reaches zero. Note that there is also a physician sample version which delivers 14 doses, which differs only in that the dose counter advances more quickly, only allowing 28 actuations to be delivered after priming. The integral counters count down to zero as the devices are used. The drug product is discarded when the counter reaches zero and the device locks, or if the device reaches an age of 3 months after the initial insertion of the cartridge. The patient instructions for use include priming instructions for initial use and for cases where specified time intervals pass since last use. The minimum fill of formulation in the cartridge is 4.0 g, which includes a large overfill to assure adequate performance. This overfill of formulation is not available to patients, however, as the devices lock when the counter reaches zero. The energy required to produce the aerosol is provided by the loading of a spring, accomplished by mechanically turning the base of the device prior to actuation, and thus, there is no propellant or traditional pump mechanism.

The drug product formulation is aqueous based, is contained in the cartridge, and is sterile, as required by regulation (21 CFR 200.51). The formulation contains (b) (4) olodaterol drug substance (b) (4) as the hydrochloride salt), as well as citric acid (b) (4) (b) (4) edetate disodium as a (b) (4) and benzalkonium chloride as a (b) (4). The formulation is packaged in a plastic container within an aluminum can (the cartridge). (b) (4)

(b) (4) he maximum use period is 3 months. With daily use as intended, the device would require replacement after 30 daily doses are obtained. Currently, the proposed expiration

dating period of 36 months for the drug product is supported by the stability data provided; however, the microbiology team will need to confirm their acceptance of this period as well.

To use the drug product, the patient first removes the clear base of the Respimat® device and inserts the cartridge containing the formulation. The clear base is replaced (b) (4)

Once inserted, the cartridge is not to be removed. The drug product is primed by actuating until a mist is visible and then an additional three times. A single repriming actuation is needed if the device is not used for more than 3 and up to 21 days. After 21 days of non-use, repriming is done as for the initial priming procedure.

To obtain a dose from the product, the device is held upright, with the yellow cap closed, and the clear base is turned in the direction of the arrows on the label until a click is heard after one-half turn. The yellow cap is opened and the patient exhales, then sealing his/her lips around the mouthpiece. While inhaling slowly and deeply, the patient actuates the device with the trigger button and continues inhaling for at least 1.5 seconds. The patient then holds his/her breath for an additional 10 seconds before exhaling. The patient is instructed to wipe the mouthpiece and metal nozzle with a damp cloth or tissue on a weekly basis for hygienic purposes.

Two actuations of the device provides a total of 5.0 mcg of olodaterol drug substance, a long acting beta agonist which is proposed for the treatment of chronic obstructive pulmonary disease (COPD) with once daily dosing.

The drug product is to be stored at controlled room temperature and must be protected from freezing to avoid damage to the cartridge containing the formulation.

Stability data support a (b) (4) month expiry.

Drug Product: Satisfactory.

Labeling:

(b) (4) container labels and package insert are acceptable.

Overall Conclusion:

From a CMC perspective, the application is recommended for approval.

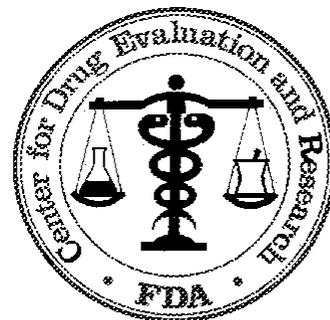
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/s/

ERIC P DUFFY
07/30/2014

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

DATE: 20-JUN-2014
TO: N203108 File
FROM: Craig M. Bertha, PhD
Acting CMC Lead
ONDQA, Division III, Branch VIII



THROUGH: Eric Duffy, PhD
Acting Branch Chief/Division Director
ONDQA, Division III, Branch VIII

SUBJECT: Update on Establishment Evaluation Request for N203108 Striverdi[®] Respimat[®]
(olodaterol inhalation spray); CMC recommendation

SUMMARY:

The Office of Compliance issued an overall recommendation of ACCEPTABLE for the application on 16-JUN-2014. The summary report from the Establishment Evaluation System is attached below.

RECOMMENDATION: Considering the recommendation from the Office of Compliance, the application is **recommended to be approved**.

Craig M. Bertha, Ph.D.
Acting CMC Lead, ONDQA

cc:
OND/DPARP/CChung
ONDQA/DIV 3/CBertha/20-JUN-2014
ONDQA/DIV 3/EDuffy
OPS/JCole
ONDQA/DIV 3/YLiu
OND/DPARP/RLim
OND/DPARP/CGalvis
OB/DBII/RAbugov

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: NDA 203108/000
Org. Code: 570
Priority: 1
Stamp Date: 14-MAY-2012
PDUFA Date: 02-AUG-2014
Action Goal:
District Goal: 03-JUN-2014

Sponsor: BOEHRINGER PHARMS
900 RIDGEBURY RD
RIDGEFIELD, CT 068770368
Brand Name: STRIVERDI RESPIMAT
Estab. Name:
Generic Name: OLODATEROL RESPIMAT INHALATION SPRAY
Product Number; Dosage Form; Ingredient; Strengths
001; SOLUTION, SPRAY; OLODATEROL HYDROCHLORIDE;
.0027MG

FDA Contacts: C. BERTHA Prod Qual Reviewer 3017961646
Y. LIU Product Quality PM 3017961926
C. CHUNG Regulatory Project Mgr (HFD-570) 3017963420
ID = 105168 Team Leader

Overall Recommendation:	ACCEPTABLE	on 16-JUN-2014	by R. SAFAAI-JAZI	()	3017964463
	PENDING	on 05-JUN-2014	by EES_PROD		
	WITHHOLD	on 11-MAR-2013	by EES_PROD		
	PENDING	on 04-MAR-2013	by EES_PROD		
	PENDING	on 04-MAR-2013	by EES_PROD		
	PENDING	on 06-FEB-2013	by EES_PROD		
	PENDING	on 21-JUN-2012	by EES_PROD		
	PENDING	on 21-JUN-2012	by EES_PROD		

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: CFN: 9610492 FEI: 3002806556
 BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG
 BINGER STREET 173
 INGELHEIM AM RHEIN, RHEINLAND-PFALZ, GERMANY

DMF No: AADA:

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

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 16-JUN-2014

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 11-JUN-2014

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

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

DMF No: AADA:

Responsibilities: FINISHED DOSAGE RELEASE TESTER
 FINISHED DOSAGE STABILITY TESTER

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 24-JAN-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

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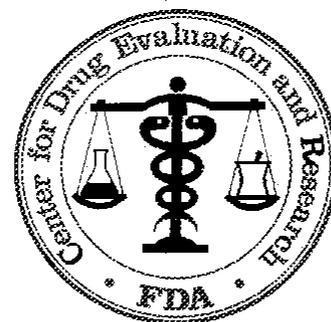
/s/

CRAIG M BERTHA
06/20/2014

ERIC P DUFFY
06/23/2014

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

DATE: 12-MAR-2013
TO: N203108 File
FROM: Craig M. Bertha, Ph.D.
Chemist
ONDQA, Division III, Branch VIII



THROUGH: Prasad Peri, Ph.D.
Branch Chief
ONDQA, Division III, Branch VIII

SUBJECT: Update on Establishment Evaluation Request for N203108 Striverdi[®] Respimat[®]
(olodaterol inhalation spray); CMC recommendation

SUMMARY:

The Office of Compliance issued an overall recommendation of WITHHOLD for the application on 11-MAR-2013. The summary report from the Establishment Evaluation System is attached below.

RECOMMENDATION: Considering the recommendation from the Office of Compliance, the application is **not recommended to be approved**.

Craig M. Bertha, Ph.D.
CMC Reviewer, ONDQA

cc:
OND/DPARP/CChung
ONDQA/DIV 3/CBertha/12-MAR-2013
ONDQA/DIV 3/EDuffy
ONDQA/DIV 3/PPeri
ONDQA/DIV33/ASchroeder
OPS/JCole
ONDQA/DIV 3/YLiu
OND/DPARP/RLim
OND/DPARP/CRivera-Lopez
OB/DBII/RAbugov

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

Application:	NDA 203108/000	Sponsor:	BOEHRINGER PHARMS
Org. Code:	570		900 RIDGEBURY RD
Priority:	1		RIDGEFIELD, CT 068770368
Stamp Date:	14-MAY-2012	Brand Name:	Striverdi Respimat
PDUFA Date:	14-MAR-2013	Estab. Name:	
Action Goal:		Generic Name:	Olodaterol Respimat Inhalation Spray
District Goal:	13-JAN-2013	Product Number; Dosage Form; Ingredient; Strengths	001; SOLUTION, SPRAY; OLODATEROL HYDROCHLORIDE; .0027MG
FDA Contacts:	Y. LIU	Project Manager	3017961926
	C. BERTHA	Review Chemist	3017961646
	A. SCHROEDER	Team Leader	3017961749

Overall Recommendation:	WITHHOLD	on 11-MAR-2013	by T. GOOEN	(HFD-320)	3017963257
	PENDING	on 04-MAR-2013	by EES_PROD		
	PENDING	on 04-MAR-2013	by EES_PROD		
	PENDING	on 06-FEB-2013	by EES_PROD		
	PENDING	on 21-JUN-2012	by EES_PROD		
	PENDING	on 21-JUN-2012	by EES_PROD		

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: CFN: 9610492 FEI: 3002806556
 BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG
 BINGER STREET 173
 INGELHEIM AM RHEIN, RHEINLAND-PFALZ, GERMANY

DMF No: AADA:

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

Profile: AEROSOL DISPERSED MEDICATION **OAI Status:** POTENTIAL OAI

Last Milestone: OC RECOMMENDATION

Milestone Date: 11-MAR-2013

Decision: WITHHOLD

Reason: DISTRICT RECOMMENDATION

Profile: (b) (4) **OAI Status:** POTENTIAL OAI

Last Milestone: OC RECOMMENDATION

Milestone Date: 11-MAR-2013

Decision: WITHHOLD

Reason: DISTRICT RECOMMENDATION

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

DMF No: AADA:

Responsibilities: FINISHED DOSAGE RELEASE TESTER
 FINISHED DOSAGE STABILITY TESTER

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 24-JAN-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

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

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

DMF No: [REDACTED] **AADA:**

Responsibilities: FINISHED DOSAGE STERILITY TESTER

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 04-MAR-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

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/s/

CRAIG M BERTHA
03/12/2013

PRASAD PERI
03/12/2013
I concur

Striverdi® Respimat® (olodaterol) Inhalation Spray

NDA 203108

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

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

Representative: Damon Daulerio, MBA

Indication: Long-term once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and/or emphysema.

Presentation:

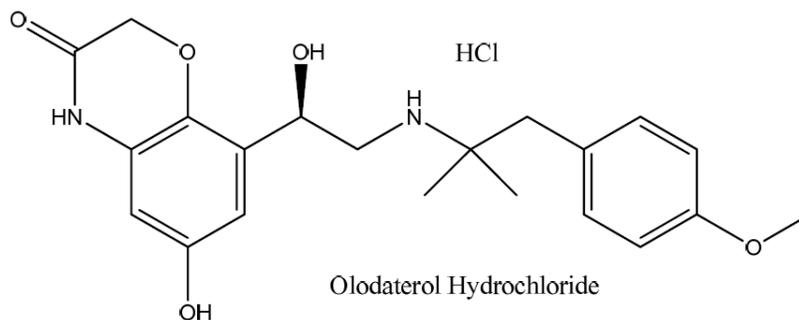
The currently supported expiry period is (b) (4) months for storage at controlled room temperature.

EER Status: Pending.

Consults: EA – Categorical exclusion granted under 21 CFR §25.31(c)
Methods Validation – Drug substance and drug product impurities methods found to be acceptable for regulatory purposes
Pharm/toxicology – Acceptable
CDRH Consult for Device – Drug product with the same device approved.

Original Submission: 14-May-2012

Drug Substance:



The drug substance olodaterol hydrochloride is a white to off-white (b) (4) solid which is

(b) (4)

The drug substance has the following specifications: Appearance, ID (b) (4), Color of Solution, Clarity of Solution, Organic Impurities, (b) (4) Purity, Residual Solvents, (b) (4) and Assay.

The container closure system consists of an (b) (4) for storage and shipping.

The drug substance has adequate stability and a retest period of (b) (4) is supported by the stability data provided. The drug substance is manufactured by Boehringer Ingelheim Pharma GmbH and Co. KG, Ingelheim am Rhein, Germany. **The EES status for this facility is a withhold status.**

Conclusion: The drug substance is not Satisfactory based on the EES status for this facility.

Drug Product:

This NDA from Boehringer Ingelheim for Striverdi® Respimat® (olodaterol) inhalation spray is the third NDA submitted for this new type of dosage form. The drug product consists of an aluminum/plastic cartridge containing a sterile aqueous formulation that is inserted in a Respimat® delivery device. The Respimat® delivery device is the same one proposed to be used for all three inhalation spray applications that have been submitted by the applicant. Once inserted by the patient, the unit must be primed prior to first use.

The current proposed once-daily dose is two actuations or inhalations from the inhaler, which delivers a total volume of formulation for both actuations of 22.1 mL, containing 5.4 mcg of olodaterol hydrochloride, which is equivalent to 5.0 mcg of olodaterol. The device delivers 60 actuations after priming for a total of 30 doses and it locks to prevent further use once these doses are delivered and dose indicator reaches zero.

Note that there is also a physician sample version which delivers 14 doses. The dose indicator counts down to zero as the devices are used. The drug product is discarded when the indicator reaches zero and the device locks, or if the device reaches an age of 3 months after the initial insertion of the cartridge.

The minimum fill of formulation in the cartridge is 4.0 g, which includes a large overfill to assure adequate performance.

The energy required to produce the aerosol is provided by the loading of a spring accomplished by mechanically turning the base of the device prior to actuation, and thus, there is no propellant or traditional pump mechanism.

The drug product formulation is aqueous based, is contained in the cartridge, and is sterile, as required by regulation (21 CFR 200.51). The formulation contains (b) (4) olodaterol drug substance (b) (4) as the hydrochloride salt), as well as citric acid (b) (4), edetate disodium as a (b) (4), and benzalkonium chloride as a (b) (4). The formulation is packaged in a plastic container within an aluminum can (the cartridge).

(b) (4)

(b) (4)

The maximum use period is 3 months. With daily use as intended, the device would require replacement after 30 daily doses are obtained. Currently, the proposed expiration dating period of 36 months for the drug product is supported by the stability data provided.

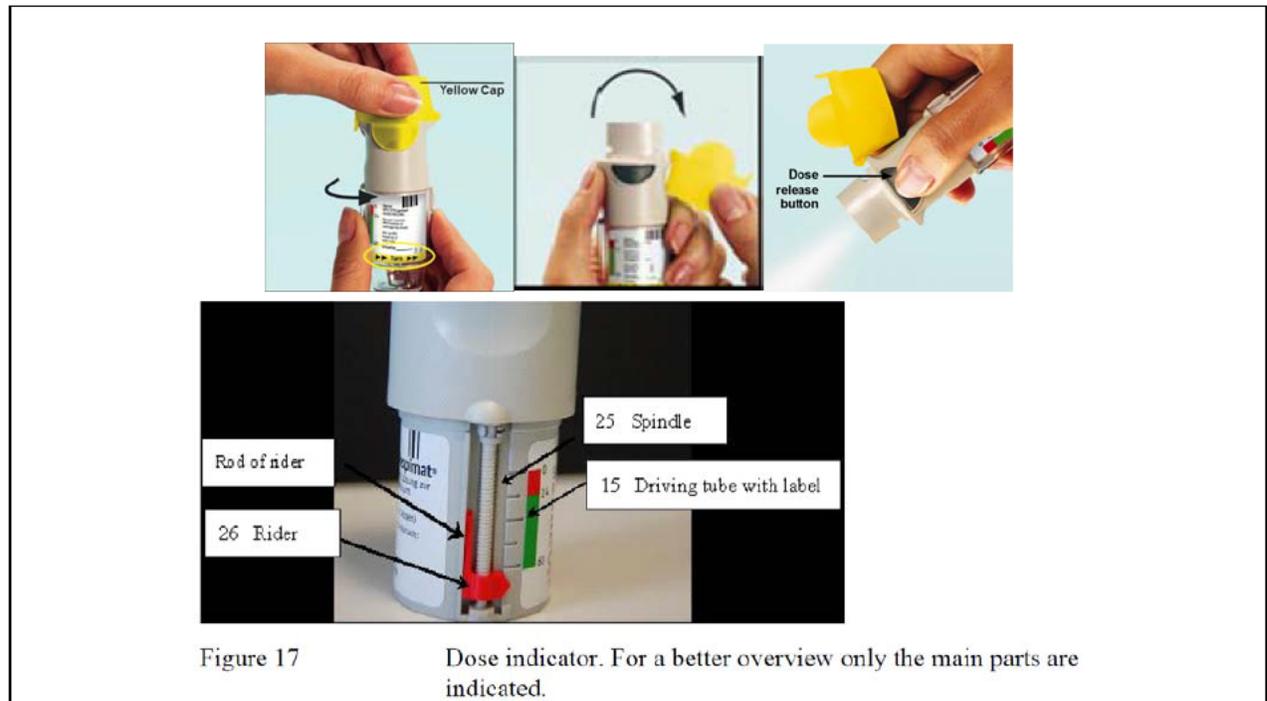
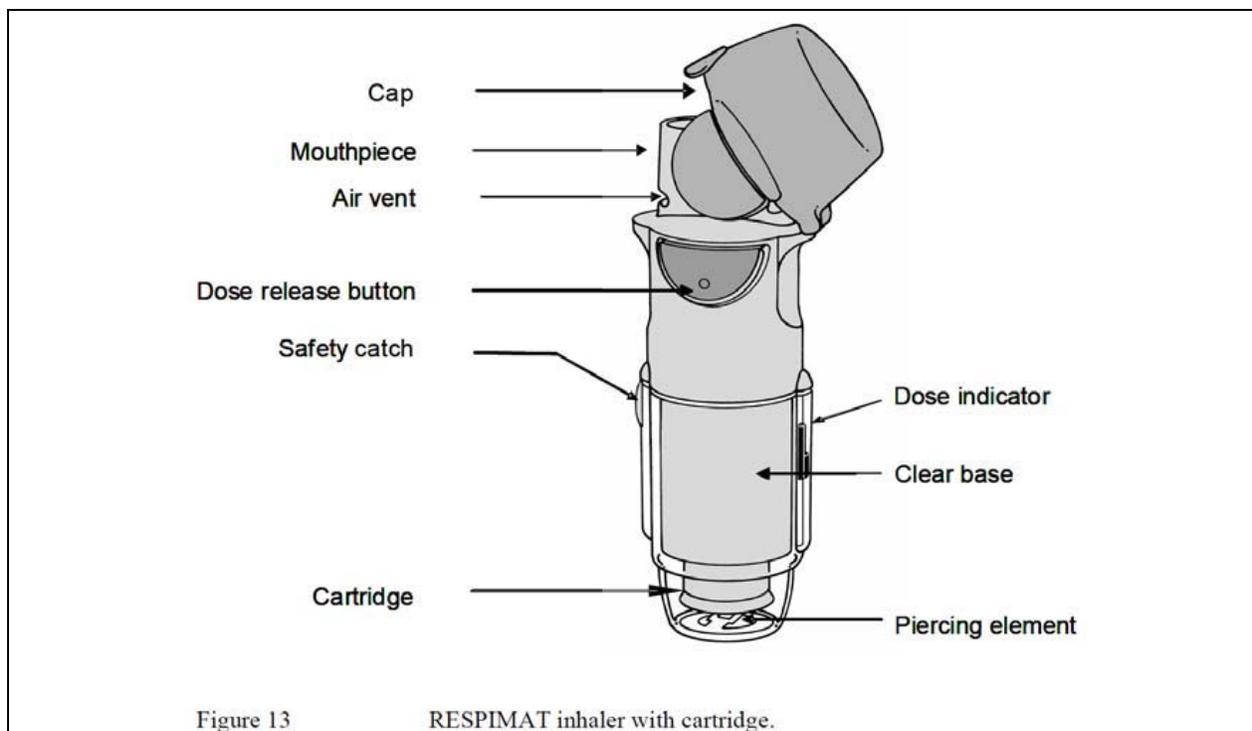


Figure 17 Dose indicator. For a better overview only the main parts are indicated.



The drug product is controlled by the instituting the following specifications: Appearance, Color of Solution, Clarity of Solution, pH, Loss of Mass, Volume of Content, Identifications, Assay, Impurities, Assay for Benzalkonium chloride and Disodium Edetate, Particulate matter, Sterility, Spray content uniformity, Pump Delivery, Number of Actuations, and Aerodynamic Particle Size Distribution.

The drug product is manufactured by Boehringer Ingelheim Pharma gmbH and Co. KG, Ingelheim am Rhein, Germany. **The EES status for this facility is a withhold due to GMP issues.**

Conclusion: The drug product is not Satisfactory based on the EES status for this facility.

Additional Items:

All associated Drug Master Files are acceptable or the pertinent information has been adequately provided in the application.

The analytical methods for determination of the drug substance and drug product impurities were sent to the Agency laboratory for assessment and were found to be adequate for regulatory purposes.

Note however that the Office of Compliance has found issues with the main manufacturing site for the drug product in relation to general GMP inspection. While this may not reflect any specific findings for this product, it may represent a failure of the Quality System for the site. Hence based on the inspection, the site is issued a warning letter for inadequate GMPs by the Office of Compliance.

Overall Conclusion: From a CMC perspective, the application is recommended for **Complete Response** since manufacturing and testing sites for the drug substance and drug product do not have an acceptable GMP recommendation from the Office of Compliance as of this writing. Proposed Language for the Action letter:

PRODUCT QUALITY

During a recent inspection of the Boehringer Ingelheim Pharma GmbH & Co. KG manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

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/s/

PRASAD PERI
03/11/2013

ERIC P DUFFY
03/11/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

METHODS VALIDATION REPORT SUMMARY

TO: Craig M. Bertha, CMC Reviewer
Office of New Drug Quality Assessment (ONDQA)
E-mail Address: craig.bertha@fda.hhs.gov
Phone: (301) 796-1646
Fax: (301) 796-9747

FROM: FDA
Division of Pharmaceutical Analysis
Michael Trehy, MVP Coordinator
Suite 1002
1114 Market Street
St. Louis, MO 63101
Phone: (314) 539-3815

Through: John Kauffman, Acting Deputy Director
Phone: (314) 539-3869

SUBJECT: Methods Validation Report Summary

Application Number: 203108

Name of Product: (b) (4) Respimat (olodaterol) Inhalation Spray

Applicant: Boehringer Ingelheim Pharmaceuticals, Inc.

Applicant's Contact Person: Damon Daulerio, MBA, Associate Director

Address: 900 Ridgebury Road, P.O. Box 368, Ridgefield, CT 06877

Telephone: (203) 482-6346 Fax: (203) 791-6262

Date Methods Validation Consult Request Form Received by DPA: 7/23/12

Date Methods Validation Package Received by DPA: 7/23/12

Date Samples Received by DPA: 9/7/12

Date Analytical Completed by DPA: 2/15/13

Laboratory Classification: 1. Methods are acceptable for control and regulatory purposes.
2. Methods are acceptable with modifications (as stated in accompanying report).
3. Methods are unacceptable for regulatory purposes.

Comments: See attached memo for results summary.



DEPARTMENT OF HEALTH & HUMAN SERVICES
Food and Drug Administration

Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis
St. Louis, MO 63101
Tel. (314) 539-2168

Date: February 15, 2013

To: Craig M. Bertha, Ph.D. and Alan Schroeder, Ph.D. Office of New Drug Quality Assessment

Through: John Kauffman, Acting Deputy Director, Division of Pharmaceutical Analysis

From: Kallol Biswas, Ph.D., Chemist

Subject: Method Validation for NDA 203108 (b)(4) Respimat (olodaterol) Inhalation Spray

The following methods were evaluated and are acceptable for quality control and regulatory purposes:

Organic Impurities - Analytical Procedure 032977-05

Assay, identification, determination of degradation products - Analytical Procedure 035324-01

Summary results in attached tables.

Data package (18 MB) including chromatograms is available at the following link.
<http://ecmsweb.fda.gov:8080/webtop/dri/objectId/090026f8803fc7da>

Results Summary

Method	Results																																																																												
<p align="center">Organic Impurities - Analytical Procedure 032977-05</p>	<p>Mean results</p> <div style="display: flex; justify-content: space-between; align-items: flex-start;"> <div style="width: 20%;"> <p>(b) (4)</p> <p>(b) (4)</p> </div> <table border="1" style="width: 60%; border-collapse: collapse;"> <tr> <td style="width: 15%;">Sample 1-1</td> <td style="width: 15%;"></td> <td style="width: 15%;"></td> <td style="width: 15%;"></td> <td style="width: 15%;"></td> <td style="width: 15%;">Specification</td> <td style="width: 15%;">Meets Spec</td> </tr> <tr> <td>Sample 1-2</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Sample 2-1</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Sample 2-2</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Average</td> <td></td> <td></td> <td></td> <td></td> <td>(b) (4)</td> <td>Yes</td> </tr> </table> <table border="1" style="width: 60%; border-collapse: collapse;"> <tr> <td style="width: 15%;">Sample 1-1</td> <td style="width: 15%;"></td> <td style="width: 15%;"></td> <td style="width: 15%;"></td> <td style="width: 15%;"></td> <td style="width: 15%;">Specification</td> <td style="width: 15%;">Meets Spec</td> </tr> <tr> <td>Sample 1-2</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Sample 2-1</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Sample 2-2</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Average</td> <td></td> <td></td> <td></td> <td></td> <td>(b) (4)</td> <td>Yes</td> </tr> </table> </div>							Sample 1-1					Specification	Meets Spec	Sample 1-2							Sample 2-1							Sample 2-2							Average					(b) (4)	Yes	Sample 1-1					Specification	Meets Spec	Sample 1-2							Sample 2-1							Sample 2-2							Average					(b) (4)	Yes
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Sample 1-1	(b) (4)				
Sample 1-2	(b) (4)				
Sample 2-1	(b) (4)				
Sample 2-2	(b) (4)				
Average	(b) (4)				

Specific (b) (4) or total impurities: (b) (4)

Result : (b) (4)

All results meet specifications

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

/s/

MICHAEL L TREHY
02/15/2013

JOHN F KAUFFMAN
02/15/2013

NDA 203108

Striverdi® Respimat® (olodaterol) Inhalation Spray

Boehringer Ingelheim Pharmaceuticals, Inc.

Craig M. Bertha, Ph.D.

**Division of New Drug Quality Assessment III for the
Division of Pulmonary, Allergy, and Rheumatology Products**

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Chemistry Review Data Sheet

1. NDA 203108
2. REVIEW #: 2
3. REVIEW DATE: 08-NOV-2012
4. REVIEWER: Craig M. Bertha, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents

N/A
Original

Document Date

14-MAY-2012

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Amendment (Response to CMC DR letter)

Document Date

02-NOV-2012

7. NAME & ADDRESS OF APPLICANT:

Name: Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road
Address: P.O. Box 368
Ridgefield, Ct 06877
Representative: Damon Daulerio, MBA, Associate Director
Telephone: 203-482-6346

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Striverdi® Respimat® (formerly (b) (4) Respimat®)

Chemistry Review Data Sheet

- b) Non-Proprietary Name (USAN): olodaterol inhalation spray
c) Code Name/# (ONDQA only): BI 1744 CL
d) Chem. Type/Submission Priority (ONDQA only):
- Chem. Type: 1
 - Submission Priority: S

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

10. PHARMACOL. CATEGORY: olodaterol is a long-acting beta₂-adrenergic agonist (LABA) indicated for treatment of chronic obstructive pulmonary disease (COPD); olodaterol is a new molecular entity (NME)

11. DOSAGE FORM: inhalation spray

12. STRENGTH/POTENCY: each spray delivers 2.7 mcg of olodaterol hydrochloride, equivalent to 2.5 mcg olodaterol, from the mouthpiece; dose is two inhalations once daily (5.0 mcg of olodaterol)

13. ROUTE OF ADMINISTRATION: oral inhalation

14. Rx/OTC DISPENSED: Rx OTC

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

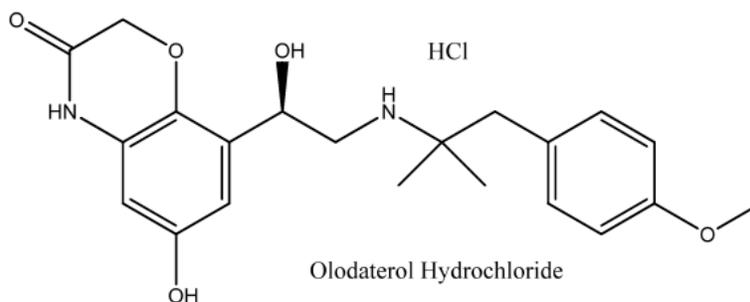
SPOTS product – Form Completed

Not a SPOTS product

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

Olodaterol hydrochloride is chiral and has the following chemical name: *2H*-1,4-Benzoxazin-3*H*(4*H*)-one, 6-hydroxy-8-[(1*R*)-1-hydroxy-2-[[2-(4-methoxyphenyl)-1,1-dimethylethyl]amino]ethyl]-, monohydrochloride. It has molecular formula C₂₁H₂₆N₂O₅·HCl and molecular mass of 422.91 g/mol (386.45 g/mol for free base). The structure is shown below:

Chemistry Review Data Sheet



17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS ³
26014	3	Boehringer Ingelheim Pharma GmbH & Co. KG	container closure for Respimat® inhaler device: (b) (4)	1	Adequate	13-JUN-2012	A microbiology review is pending however
26015	3	Boehringer Ingelheim microParts GmbH	Respimat® inhaler device	1	Adequate	13-JUN-2012	
(b) (4)	3	(b) (4)	(b) (4)	3	Adequate	31-AUG-2011	(b) (4)
	3			3	Adequate	17-MAY-2011	

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)

³ Include reference to location in most recent CMC review

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS

Chemistry Review Data Sheet

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
IND	76362	Boehringer Ingelheim Pharmaceuticals, Inc.	IND for olodaterol inhalation spray
NDA	21747	Boehringer Ingelheim Pharmaceuticals, Inc.	NDA for Combivent® Respimat® Inhalation Spray
NDA	21936	Boehringer Ingelheim Pharmaceuticals, Inc.	NDA for Spiriva® Respimat® Inhalation Spray

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics	N/A			
EES	Site inspections	21-JUN-2012	Pending	
Pharm/Tox	Consult for drug substance impurity	05-JUN-2012	Final/Carol Rivera-Lopez, Ph.D.	The limit of up to (b) (4) for the (b) (4) of the drug substance is acceptable. See consult review of 27-JUN-2012.
Biopharm	N/A			
LNC	N/A			
Methods Validation	Drug substance and drug product impurities methods	19-JUL-2012	Pending	The drug substance is an NME
OPDRA	N/A			
EA				
Microbiology	Sterilization validation, (b) (4) effectiveness test results, (b) (4) content, endotoxin controls, microbiological aspects of drug substance and product specifications	24-MAY-2012	Pending/Jessica Cole, Ph.D.	Dr. Cole is reviewing both NDA 203108 and the associated DMF 26014 for the cartridge portion of the device
OSE	labeling	DPARP to consult		
DDMAC	labeling	DPARP to consult		

The Chemistry Review for NDA 203108

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is considered to be **approvable** pending a satisfactory recommendation from the Office of compliance, and a satisfactory recommendation from the microbiology team.

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

None at this time

II. Summary of Chemistry Assessments

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

This NDA from Boehringer Ingelheim for Striverdi® Respimat® (olodaterol inhalation spray) is the third NDA submitted for this new type of dosage form. The drug product consists of an aluminum/plastic cartridge containing a sterile aqueous formulation that is inserted in a Respimat® delivery device. The Respimat® delivery device is the same one proposed to be used for all three inhalation spray applications that have been submitted by the applicant. Once inserted by the patient, the unit must be primed prior to first use. Patients need to be cautious and not subject the cartridges to freezing conditions, which would damage the cartridge. The current proposed once-daily dose is two actuations or inhalations from the inhaler, which delivers a total volume of formulation for both actuations of 22.1 mL, containing 5.4 mcg of olodaterol hydrochloride, which is equivalent to 5.0 mcg of olodaterol. The device delivers 60 actuations after priming for a total of 30 doses and it locks to prevent further use once these doses are delivered and counter reaches zero. Note that there is also a physician sample version which delivers 14 doses, which differs only in that the dose counter advances more quickly, only allowing 28 actuations to be delivered after priming. The integral counters count down to zero as the devices are used. The drug product is discarded when the counter reaches zero and the device locks, or if the device reaches an age of 3 months after the initial insertion of the cartridge. The patient instructions for use include priming instructions for initial use and for cases where specified time intervals pass since last use. The minimum fill of formulation in the cartridge is 4.0 g, which includes a large overfill to assure adequate performance. This overfill of formulation is not available to patients, however, as the devices lock when the counter reaches zero. The energy required to produce the aerosol is provided by the loading of a spring, accomplished by mechanically turning the base of the device prior to actuation, and thus, there is no propellant or traditional pump mechanism.

The drug product formulation is aqueous based, is contained in the cartridge, and is sterile, as required by regulation (21 CFR 200.51). The formulation contains (b) (4) olodaterol drug substance (b) (4) as the hydrochloride salt), as well as citric acid (b) (4) (b) (4) edetate disodium as a (b) (4) and benzalkonium chloride as a (b) (4). The formulation is packaged in a plastic container within an aluminum can (th (b) (4)

(b) (4) (b) (4) The maximum use period is 3 months. With daily use as intended, the device would require replacement after 30 daily doses are obtained. Currently, the proposed expiration dating period of 36 months for the drug product is supported by the stability data provided; however, the microbiology team will need to confirm their acceptance of this period as well.

The drug substance olodaterol hydrochloride is a white to off-white (b) (4) solid that is (b) (4)

(b) (4) (b) (4) The drug substance is not (b) (4) (b) (4) The drug substance has adequate stability and a retest period of (b) (4) is supported by the stability data provided.

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

To use the drug product, the patient first removes the clear base of the Respimat® device and inserts the cartridge containing the formulation. The clear base is replaced (b) (4) (b) (4)

(b) (4). Once inserted, the cartridge is not to be removed. The drug product is primed by actuating until a mist is visible and then an additional three times. A single repriming actuation is needed if the device is not used for more than 3 and up to 21 days. After 21 days of non-use, repriming is done as for the initial priming procedure.

To obtain a dose from the product, the device is held upright, with the yellow cap closed, and the clear base is turned in the direction of the arrows on the label until a click is heard after one-half turn. The yellow cap is opened and the patient exhales, then sealing his/her lips around the mouthpiece. While inhaling slowly and deeply, the patient actuates the device with the trigger button and continues inhaling for at least 1.5 seconds. The patient then holds his/her breath for an additional 10 seconds before exhaling. The patient is instructed to wipe the mouthpiece and metal nozzle with a damp cloth or tissue on a weekly basis for hygienic purposes.

Two actuations of the device provides a total of 5.0 mcg of olodaterol drug substance, a long acting beta agonist which is proposed for the treatment of chronic obstructive pulmonary disease (COPD) with once daily dosing.

The drug product is to be stored at controlled room temperature and must be protected from freezing to avoid damage to the cartridge containing the formulation.

C. Basis for Approvability or Not-Approval Recommendation

The application is considered to be **approvable**. A recommendation for approval will require a satisfactory recommendation from both the microbiology team as well as the Office of Compliance. The applicant has also committed to make changes to the package insert as outlined in comment 14.a of the CMC discipline review letter, in the next revised submission of labeling.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Craig M. Bertha, Ph.D./ONDQA/DNDQA III/Branch VIII/11/08/12
Prasad Peri, Ph.D. /ONDQA/DNDQA III/Branch VIII

C. CC Block

Christine Chung/OND/DPARP
Robert Lim/OND/DPARP
Carol Rivera-Lopez/OND/DPARP
Robert Abugov/OB/DBII
Alan Schroeder/ONDQA/DNDQA III/Branch VIII
Youbang Liu/ONDQA/DNDQA III
Jessica Cole/OPS

13 Page(s) has 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/

CRAIG M BERTHA
11/08/2012

PRASAD PERI
11/08/2012
I concur

NDA 203108

(b) (4)

Respimat® (olodaterol) Inhalation Spray

Boehringer Ingelheim Pharmaceuticals, Inc.

Craig M. Bertha, Ph.D.

**Division of New Drug Quality Assessment III for the
Division of Pulmonary, Allergy, and Rheumatology Products**

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Chemistry Review Data Sheet

1. NDA 203108
2. REVIEW #: 1
3. REVIEW DATE: 23-JUL-2012
4. REVIEWER: Craig M. Bertha, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

N/A

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original

Document Date

14-MAY-2012

7. NAME & ADDRESS OF APPLICANT:

Name: Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road
Address: P.O. Box 368
Ridgefield, Ct 06877
Representative: Damon Daulerio, MBA, Associate Director
Telephone: 203-482-6346

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: (b) (4) Respimat®

Chemistry Review Data Sheet

- b) Non-Proprietary Name (USAN): olodaterol inhalation spray
c) Code Name/# (ONDQA only): BI 1744 CL
d) Chem. Type/Submission Priority (ONDQA only):
- Chem. Type: 1
 - Submission Priority: S

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

10. PHARMACOL. CATEGORY: olodaterol is a long-acting beta₂-adrenergic agonist (LABA) indicated for treatment of chronic obstructive pulmonary disease (COPD); olodaterol is a new molecular entity (NME)

11. DOSAGE FORM: inhalation spray

12. STRENGTH/POTENCY: each spray delivers 2.7 mcg of olodaterol hydrochloride, equivalent to 2.5 mcg olodaterol, from the mouthpiece; dose is two inhalations once daily (5.0 mcg of olodaterol)

13. ROUTE OF ADMINISTRATION: oral inhalation

14. Rx/OTC DISPENSED: Rx OTC

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

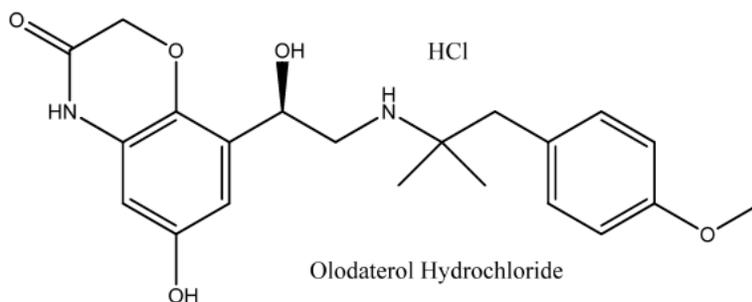
SPOTS product – Form Completed

Not a SPOTS product

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

Olodaterol hydrochloride is chiral and has the following chemical name: *2H*-1,4-Benzoxazin-3*H*(4*H*)-one, 6-hydroxy-8-[(1*R*)-1-hydroxy-2-[[2-(4-methoxyphenyl)-1,1-dimethylethyl]amino]ethyl]-, monohydrochloride. It has molecular formula C₂₁H₂₆N₂O₅ HCl and molecular mass of 422.91 g/mol (386.45 g/mol for free base). The structure is shown below:

Chemistry Review Data Sheet



17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS ³
26014	3	Boehringer Ingelheim Pharma GmbH & Co. KG	container closure for Respimat® inhaler device: (b) (4)	1	Adequate	13-JUN-2012	
26015	3	Boehringer Ingelheim microParts GmbH	Respimat® inhaler device	1	Adequate	13-JUN-2012	
(b) (4)	3	(b) (4)	(b) (4)	3	Adequate	31-AUG-2011	(b) (4)
	3			3	Adequate	17-MAY-2011	

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)

³ Include reference to location in most recent CMC review

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS

Chemistry Review Data Sheet

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
IND	76362	Boehringer Ingelheim Pharmaceuticals, Inc.	IND for olodaterol inhalation spray
NDA	21747	Boehringer Ingelheim Pharmaceuticals, Inc.	NDA for Combivent® Respimat® Inhalation Spray
NDA	21936	Boehringer Ingelheim Pharmaceuticals, Inc.	NDA for Spiriva® Respimat® Inhalation Spray

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics	N/A			
EES	Site inspections	21-JUN-2012	Pending	
Pharm/Tox	Consult for drug substance impurity	05-JUN-2012	Final/Carol Rivera-Lopez, Ph.D.	The limit of up to (b) (4) for the (b) (4) of the drug substance is acceptable. See consult review of 27-JUN-2012.
Biopharm	N/A			
LNC	N/A			
Methods Validation	Drug substance and drug product impurities methods	19-JUL-2012	Pending	The drug substance is an NME
OPDRA	N/A			
EA				
Microbiology	Sterilization validation, (b) (4) effectiveness test results (b) (4) content, endotoxin controls, microbiological aspects of drug substance and product specifications	24-MAY-2012	Pending/Jessica Cole, Ph.D.	
OSE	labeling	DPARP to consult		
DDMAC	labeling	DPARP to consult		

The Chemistry Review for NDA 203108

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is considered to be **approvable** pending a satisfactory recommendation from the Office of compliance, a satisfactory recommendation from the microbiology team, and pending the resolution of the CMC-related issues outlined in the attached draft discipline review letter.

It is requested that the PM send the comments in the attached discipline review letter (see p. 155) to the applicant.

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

None at this time

II. Summary of Chemistry Assessments

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

This NDA from Boehringer Ingelheim for (b) (4) Respimat® (olodaterol inhalation spray) is the third NDA submitted for this new type of dosage form. The drug product consists of an aluminum/plastic cartridge containing a sterile aqueous formulation that is inserted in a Respimat® delivery device. The Respimat® delivery device is the same one proposed to be used for all three inhalation spray applications that have been submitted by the applicant. Once inserted by the patient, the unit must be primed prior to first use. Patients need to be cautious and not subject the cartridges to freezing conditions, which would damage the cartridge. The current proposed once-daily dose is two actuations or inhalations from the inhaler, which delivers a total of 22.1 mL of formulation containing 5.4 mcg of olodaterol hydrochloride, which is equivalent to 5.0 mcg of olodaterol. The device delivers 60 actuations after priming for a total of 30 doses and it locks to prevent further use once these doses are delivered and counter reaches zero. Note that there is also a physician sample version which delivers 14 doses, which differs only in that the dose counter advances more quickly, only allowing 28 actuations to be delivered after priming. The integral counters count down to zero as the devices are used. The drug product is discarded when the counter reaches zero and the device locks, or if the device reaches an age of 3 months after the initial insertion of the cartridge. The patient instructions for use include priming instructions for initial use and for cases where specified time intervals pass since last use. The minimum fill of formulation in the cartridge is 4.0 g, which includes a large overfill to assure adequate performance. This overfill of formulation is not available to patients, however, as the devices lock when the counter reaches zero. The energy required to produce the aerosol is provided by the loading of a spring, accomplished by mechanically turning the base of

the device prior to actuation, and thus, there is no propellant or more traditional pump mechanism.

The drug product formulation is aqueous based, is contained in the cartridge, and is sterile, as required by regulation (21 CFR 200.51). The formulation contains (b) (4) olodaterol drug substance (b) (4) as the hydrochloride salt), as well as citric acid (b) (4) (b) (4) edetate disodium as a (b) (4) and benzalkonium chloride as a (b) (4). The formulation is packaged in a plastic container within an aluminum can (the cartridge). (b) (4)

(b) (4)
The maximum use period is 3 months. With daily use as intended, the device would require replacement after 30 daily doses are obtained. Currently, the proposed expiration dating period of 36 months for the drug product is supported by the stability data provided; however, the microbiology team will need to confirm their acceptance of this period as well.

The drug substance olodaterol hydrochloride is a white to off-white (b) (4) solid that is (b) (4)
(b) (4)
The drug substance has adequate stability and a retest period of (b) (4) is supported by the stability data provided.

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

To use the drug product, the patient first removes the clear base of the Respimat® device and inserts the cartridge containing the formulation. The clear base is replaced (b) (4)

Once inserted, the cartridge is not to be removed. The drug product is primed by actuating until a mist is visible and then an additional three times. A single repriming actuation is needed if the device is not used for more than 3 and up to 21 days. After 21 days of non-use, repriming is done as for the initial priming procedure.

To obtain a dose from the product, the device is held upright, with the yellow cap closed, and the clear base is turned in the direction of the arrows on the label until a click is heard after one-half turn. The yellow cap is opened and the patient exhales, then sealing his/her lips around the mouthpiece. While inhaling slowly and deeply, the patient actuates the device with the trigger

button and continues inhaling for at least 1.5 seconds. The patient then holds his/her breath for an additional 10 seconds before exhaling. The patient is instructed to wipe the mouthpiece and metal nozzle with a damp cloth or tissue on a weekly basis for hygienic purposes.

Two actuations of the device provides a total of 5.0 mcg of olodaterol drug substance, a long acting beta agonist which is proposed for the treatment of chronic obstructive pulmonary disease (COPD) with once daily dosing.

The drug product is to be stored at controlled room temperature and must be protected from freezing to avoid damage to the cartridge containing the formulation.

C. Basis for Approvability or Not-Approval Recommendation

The application is considered to be **approvable** pending the resolution of the issues outlined in the attached draft discipline review letter at the end of this review (see p. 155). Approval will also require a satisfactory recommendation from both the microbiology team as well as the Office of Compliance.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Craig M. Bertha, Ph.D./ONDQA/DNDQA III/Branch VIII/7/23/12
Prasad Peri, Ph.D. /ONDQA/DNDQA III/Branch VIII

C. CC Block

Christine Chung/OND/DPARP
Robert Lim/OND/DPARP
Carol Rivera-Lopez/OND/DPARP
Robert Abugov/OB/DBII
Alan Schroeder/ONDQA/DNDQA III/Branch VIII
Youbang Liu/ONDQA/DNDQA III
Jessica Cole/OPS

158 Page(s) has 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/

CRAIG M BERTHA
07/30/2012

PRASAD PERI
07/31/2012
I concur

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

NDA #: 203108

Received Date: 14 May 2012

APPLICATION INFORMATION

1. NEW DRUG APPLICATION NUMBER: 203108

2. Drug Name: (b) (4) Respiamat (olodaterol inhalation spray)

[Code Name: BI 1744 CL]

3. RECEIVED DATE: 5/14/12

4. RELATED REVIEW DOCUMENTS:

a. Drug Master Files listed on 356h form:

DMF #	TYP E	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	III	(b) (4)	(b) (4)	10/30/08	
(b) (4)	III	(b) (4)	(b) (4)	9/20/11	
(b) (4)	III	(b) (4)	(b) (4)	to be updated with DMF #	
(b) (4)	III	(b) (4)	(b) (4)	to be updated with DMF #	

[note: the last two DMFs did not yet have assigned numbers by the FDA when they were submitted]

b. Recommended Consults

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics	<input type="checkbox"/>	X	May not need to be requested based upon the stability data summary and lack of trending in general (except for (b) (4) the main degradant).

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Clin Pharm	<input type="checkbox"/>	X	
EES	X	<input type="checkbox"/>	entered by the ONDQA Project Manager on 6/21/12
Pharm/Tox	X	<input type="checkbox"/>	Dr. Bertha submitted on 6/5/12 a pharm/tox consult for review of a drug substance impurity ^(b) ₍₄₎ of the drug substance). Leachables in the drug product may be at levels too low to require pharm/tox assessment: that should be determined.
Methods Validation	X	<input type="checkbox"/>	At least one method should be sent to the St. Louis laboratory for verification since the NDA is for an NME.
EA	X	<input type="checkbox"/>	To be reviewed by Dr. Bertha, Senior CMC Reviewer
New Drug Micro	X	<input type="checkbox"/>	Consult was submitted on May 24, 2012. (See filing review checklist in this IQA)
CDRH	<input type="checkbox"/>	<input type="checkbox"/>	to be determined after ONDQA policy check
Other	<input type="checkbox"/>	<input type="checkbox"/>	

c. Other Applications or Submissions to note (if any):

DOCUMENT NAME	DATE	APPLICATION NUMBER	DESCRIPTION
Orig. NDA	12/12/2001	N21395	Spiriva Handihaler
Orig. NDA	11/16/2007	N21936	Spiriva Respimat
Orig. NDA	10/07/2008	N21747	Combivent Respimat
Orig. IND	1/26/2007	I76362	Olodaterol

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		the drug substance that is provided in S.2.2 to include <div style="background-color: gray; width: 100px; height: 15px; margin: 5px 0;"></div> [Deficiency from Dr. Bertha's draft review.]
--	--	--

Does the submission contain any of the following elements?

	Yes	No	Comments
Botanical Products	<input type="checkbox"/>	<input type="checkbox"/>	
Combination Products	X	<input type="checkbox"/>	
Nanotechnology	<input type="checkbox"/>	<input type="checkbox"/>	
PET	<input type="checkbox"/>	<input type="checkbox"/>	
QbD Elements	<input type="checkbox"/>	<input type="checkbox"/>	
SPOTS	<input type="checkbox"/>	<input type="checkbox"/>	

Is a team review recommended?

Yes	No	Suggested expertise for team
<input type="checkbox"/>	X	

CMC Summary: Critical Issues and Complexities

Dr. Craig Bertha has at this time drafted a review of the drug substance section of this NDA for this ^{(b) (4)} New Molecular Entity and he hasn't found any significant issues from a CMC regulatory standpoint. The drug substance has been adequately characterized using a variety of analytical techniques including NMR, MS, IR, UV, X-ray powder diffraction, ^{(b) (4)}

^{(b) (4)} The applicant has performed extensive work to demonstrate the ^{(b) (4)} of impurities in the drug substance ^{(b) (4)}

^{(b) (4)} Drug substance specifications are adequate from a control standpoint. There are no major deficiencies in the analytical methods, but some clarifications will be requested. Stability data demonstrate that the drug substance is very stable (e.g., total drug related impurities in both the accelerated and long term stability conditions did not exceed ^{(b) (4)}

It is not clear whether the ^{(b) (4)} was used for drug substance used to make any clinical batches of drug product, or for the toxicology batch(es). If so, comparative data for the ^{(b) (4)}

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(b) (4) may be needed, including impurity profiles. It is noted, however, that the (b) (4) is claimed to give better quality drug substance.

The drug product, an inhalation spray, uses the Respimat A5 inhalation device (28 or 60 actuations) to produce the aqueous aerosol dose. (b) (4)

The excipients are said to meet the requirements of the appropriate USP/NF monographs. The drug formulation in a cartridge is manufactured to (b) (4)

A dose of product consists of two 2.5 mcg olodaterol actuations. The (b) (4) version of the Respimat is known to the FDA from previous NDA applications from the same applicant (i.e., these NDAs are for Combivent Respimat and Spiriva Respimat). There is a new presentation of the A5 for this application which locks out after 28 actuations although it appears to be otherwise identical to the 60 actuation Respimat A5 which is also proposed in this NDA. Other changes made in the A5 inhaler are minor and were found adequate in Dr. Bertha's review of DMF 26015 (document entered into DARRTS on 6/13/12). The Respimat device contains an actuation counter.

The applicant has performed characterization studies for the drug product, as listed in the "Guidance for Industry - Nasal Spray and Inhalation Solution, Suspension and Spray Drug Products – Chemistry, Manufacturing and Controls Documentation guidance." Drug Product returned from the clinic was evaluated, and the applicant states that the results from multiple Respimat drug products has established its ruggedness.

Drug product specifications include the attributes listed in the "Guidance for Industry, Nasal Spray and Inhalation Solution, Suspension and Spray Drug Products – Chemistry, Manufacturing and Controls Documentation," except for the following attributes: (b) (4)

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[REDACTED] (b) (4)

A drug product batch consists of [REDACTED] (b) (4)

The applicant mentions a previous agreement with the FDA for the Combivent Respimat drug product, because of the following fact. [REDACTED] (b) (4)

[REDACTED]

[REDACTED] (b) (4)

[REDACTED] (b) (4)

If the materials of the proposed drug product (especially the cartridge) have not changed [REDACTED] (b) (4), and the formulation is similar (except for the active ingredient), then it may simplify or obviate pharm/tox review of the levels of leachables in the drug product on stability. The applicant has assessed leachables in clinical phase III batches of olodaterol Respimat, which were found to be less than [REDACTED] (b) (4)

[REDACTED] The applicant has stated that none of the

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detected extractables were found as potential leachables.

The proposed expiration dating period (expiry) for the drug product is 36 months, and stability data will be evaluated to determine if this is supported. The applicant has provided drug product data for 3 primary stability batches (24 months at 25°C/60%RH and 6 months at 40°C/75%RH), and one batch of the 28 actuation physician sample (6 months at 40°C/75%RH). The three primary stability batches are production scale batches (b) (4) and are said to be “fully representative of the container closure system used in pivotal clinical studies and intended for commercial use.” The container closure system includes the cartridge and the inhaler device. The applicant claims that the provided in-use stability data support a proposed 3 month in-use shelf life after the cartridge is inserted into the inhaler, these data are also to be evaluated.

Description of Facility Related Risks or Complexities (i.e. foreign sites, large number of sites involved, etc.)

See EES for complete list of facilities related to this application.

Selected Information (copied from the NDA):

Structural formula of the drug substance:

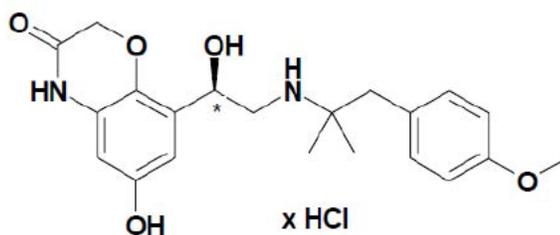


Figure 1

Structure of the drug substance olodaterol CL (b) (4)

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Photo or drawing of the device and cartridge:

[Figure 3](#) shows the RESPIMAT inhaler with the cartridge inserted and the aerosol plume generated. The cartridge alone is shown in [Figure 4](#).

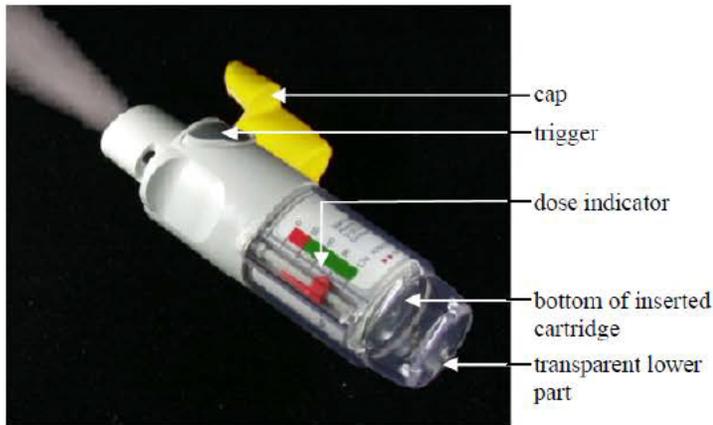


Figure 3

Olodaterol RESPIMAT Inhalation
Spray inhaler with cartridge inserted
and aerosol generated

Figure 4 Cartridge (shown
without labeling
text)

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Drug substance specifications:

Table 5 Specification and analytical procedures for olodaterol CL drug substance

Test parameter	Acceptance criteria	Analytical procedure
Appearance	White to off-white powder	Visual test
Identification IR spectrum	(b) (4)	
(b) (4) purity		
Melting point		
Test for chloride		
Colour of solution		
Clarity of solution		
Organic impurities		
(b) (4)		
Any unspecified impurity		
Total impurities		
(b) (4) purity		
(b) (4)		
Residual solvents		
(b) (4)		
(b) (4)		
Catalysts		
(b) (4)		
(b) (4)		
Assay		

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Composition of the drug product:

Table 8 Qualitative and quantitative composition of olodaterol RESPIMAT inhalation spray

Name of ingredient	Per actuation ⁴⁾ [mg]	Percentage formula [g/100mL]	Per cartridge 4.5 mL ⁵⁾ [mg]	Function	Reference to standards
Olodaterol hydrochloride (corresponds to Olodaterol ¹⁾)	0.0027	(b) (4)	(b) (4)	Drug substance	Company standard
Benzalkonium chloride solution ²⁾ (corresponds to Benzalkonium chloride ³⁾)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	NF
Edetate disodium	(b) (4)	(b) (4)	(b) (4)	(b) (4)	USP
Anhydrous citric acid	(b) (4)	(b) (4)	(b) (4)	(b) (4)	USP
Water for Injection	(b) (4)	(b) (4)	(b) (4)	(b) (4)	USP
Total mass	(b) (4)	(b) (4)	(b) (4)	-	-

(b) (4)	q.s.	q.s.	q.s.	(b) (4)	NF
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Drug product specifications:

Table 15 Proposed regulatory specifications for olodaterol RESPIMAT inhalation spray

Test parameter	Procedure (method no.)	Acceptance criteria
Appearance		(b) (4)
Colour of solution		
Clarity of solution		
pH		
Loss of mass		
Volume of contents		
Identification		
Assay		
Impurities		
Content of benzalkonium chloride		
Content of disodium edetate		

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Test parameter	Procedure	Acceptance criteria
Particulate matter	(b) (4)	
Sterility		
Spray Content Uniformity		
Pump Delivery		
Number of Actuations		

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Test Parameter	Analytical Procedure [Method number]	Acceptance Criteria
Aerodynamic Particle Size Distribution	(b) (4)	

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Quality target product profile and critical quality attributes of the drug product:

Table 9 QTPP and CQA for olodaterol RESPIMAT Inhalation Spray

QTPP Element	Target	DP CQA
Route of administration	Inhalation	--
Dosage form	RESPIMAT Inhalation spray / Inhalation solution	--
Dose regimen and strength	One dose consisting of two actuations once per day One actuation consists of 2.5 µg olodaterol	Spray content uniformity
Container closure system	RESPIMAT inhaler for aqueous solutions generating inhalable spray: -RESPIMAT A5 with 60 actuations -RESPIMAT A5 with 28 actuations (physician samples) Container closure for RESPIMAT aqueous solutions	Spray content uniformity Aerodynamic particle size distribution
Drug product quality	Sterile solution containing the dissolved drug substance	Microbiological quality
	Inhaler delivering an inhalable Spray over the labeled number of actuations	Spray content uniformity Aerodynamic particle size distribution
	Stable for at least 36 months in climatic zones I/II In-use time: 3 months	Purity Microbiological quality

FILING REVIEW CHECKLIST

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

A. GENERAL					
	Parameter	Yes	No	N/A	Comment
1.	Is the CMC section organized adequately?	X	<input type="checkbox"/>	<input type="checkbox"/>	
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X	<input type="checkbox"/>	<input type="checkbox"/>	

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3.	Are all the pages in the CMC section legible?	x	<input type="checkbox"/>	<input type="checkbox"/>	
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Many CMC comments were sent to the IND, and these are deemed to be review issues for the reviewer to evaluate, not filing issues. See the list of previous CMC communications with the applicant, earlier in this review.

B. FACILITIES*					
	Parameter	Yes	No	N/A	Comment
5	Is a single, comprehensive list of all involved facilities available in one location in the application?	x	<input type="checkbox"/>	<input type="checkbox"/>	Attachment to Form 356h
6	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.	<input type="checkbox"/>	<input type="checkbox"/>	x	

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7	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X	<input type="checkbox"/>	<input type="checkbox"/>	
8	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X	<input type="checkbox"/>	<input type="checkbox"/>	

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9	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X	<input type="checkbox"/>		
1	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X	<input type="checkbox"/>	<input type="checkbox"/>	

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT					
	Parameter	Yes	No	N/A	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	X	<input type="checkbox"/>	<input type="checkbox"/>	

D. MASTER FILES (DMF/MAF)					
	Parameter	Yes	No	N/A	Comment
12.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X	<input type="checkbox"/>	<input type="checkbox"/>	<i>See table on cover page.</i> This is based on the NDA cross-references to the new DMFs. The NDA indicates that both the device and the complete container components are described in the DMFs. The drug substance is described in the NDA. The adequacy of the DMFs is a review issue.

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E. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)					
	Parameter	Yes	No	N/A	Comment
13.	Does the section contain a description of the DS manufacturing process?	X	<input type="checkbox"/>	<input type="checkbox"/>	
14.	Does the section contain identification and controls of critical steps and intermediates of the DS(in process parameters)?	X	<input type="checkbox"/>	<input type="checkbox"/>	
15.	Does the section contain information on impurities?	X	<input type="checkbox"/>	<input type="checkbox"/>	
16.	Does the section contain information regarding the characterization of the DS?	X	<input type="checkbox"/>	<input type="checkbox"/>	
17.	Does the section contain controls for the DS?	X	<input type="checkbox"/>	<input type="checkbox"/>	
18.	Has stability data and analysis been provided for the drug substance?	X	<input type="checkbox"/>	<input type="checkbox"/>	Statistical analysis was not provided and is not needed; parameters did not show any trending.
19.	Does the application contain Quality by Design (QbD) information regarding the DS?	<input type="checkbox"/>	X	<input type="checkbox"/>	
20.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?	<input type="checkbox"/>	X	<input type="checkbox"/>	
21.	Does the section contain container and closure information?	X	<input type="checkbox"/>	<input type="checkbox"/>	

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F. DRUG PRODUCT (DP)					
	Parameter	Yes	No	N/A	Comment
22.	Does the section contain quality controls of excipients?	X	<input type="checkbox"/>	<input type="checkbox"/>	Controls for excipients are all referenced to USP/NF monographs. There are no novel excipients in the drug product formulation.
23.	Does the section contain information on composition?	X	<input type="checkbox"/>	<input type="checkbox"/>	
24.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X	<input type="checkbox"/>	<input type="checkbox"/>	In addition to the description, 3 executed batch records are included.
25.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X	<input type="checkbox"/>	<input type="checkbox"/>	Critical steps and critical process parameters are described. Analytical methods and method validation are not provided and not required for this process. (b) (4)
26.	Is there a batch production record and a proposed master batch record?	X	<input type="checkbox"/>	<input type="checkbox"/>	There are three executed batch records in English translation (in Section 3.2.R). However, I have not found a master batch record.
27.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X	<input type="checkbox"/>	<input type="checkbox"/>	There are no manufacturing differences between clinical phase III batches and primary stability batches. Clinical batches were manufactured with a batch size of (b) (4) at the commercial manufacturing site. This is the minimum commercial batch size proposed. I don't see any information in Section 3.2.P.2 about formulations used prior to phase III clinical studies.
28.	Have any biowaivers been requested?	<input type="checkbox"/>	X	<input type="checkbox"/>	
29.	Does the section contain description of to-be-marketed container/closure system and presentations?	X	<input type="checkbox"/>	<input type="checkbox"/>	This information is referenced to DMFs 26015 and 26014, both found adequate in reviews by Dr. Craig Bertha (DARRTS date 6/13/12 for each).
30.	Does the section contain controls of the final drug product?	X	<input type="checkbox"/>	<input type="checkbox"/>	

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31.	Has stability data and analysis been provided to support the requested expiration date?	X	<input type="checkbox"/>	<input type="checkbox"/>	Three production scale primary stability batches with 24 months data at 25 deg./60% RH are provided to support a claimed 36 month expiry. Six months accelerated data (40°/75%RH) are also provided for these three batches. This is for the proposed commercial product (60 actuations). A statistical analysis is performed for solution parameters (assay and main degradant, ^{(b)(4)} ; statistical analysis for other parameters is said not to be needed due to lack of trending over time. There are only 6 months of accelerated stability data available for one physician's sample batch (28 actuation); however the only difference is the change in the counter and in the lock out point: the cartridge appears to be the same as the commercial product (assuming the same cartridge fill volume). Therefore there may not be a need for additional stability data with the physician's sample: this is deemed to be low risk.
32.	Does the application contain Quality by Design (QbD) information regarding the DP?	<input type="checkbox"/>	X	<input type="checkbox"/>	None seen so far in the NDA.
33.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?	<input type="checkbox"/>	X	<input type="checkbox"/>	None seen so far in the NDA

G. METHODS VALIDATION (MV)					
	Parameter	Yes	No	N/A	Comment
34.	Is there a methods validation package?	X	<input type="checkbox"/>	<input type="checkbox"/>	Samples and their CoA's will be provided upon FDA's request.

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H. MICROBIOLOGY					
	Parameter	Yes	No	N/A	Comment
35.	If appropriate, is a separate microbiological section included discussing sterility of the drug product?	X	<input type="checkbox"/>	<input type="checkbox"/>	Section P.2.5 (microbiological attributes), P.3.3 (sterile aspects of manufacturing process), see also P.3.4 (controls of critical steps...) and P.3.5 (sterilization process validation), P.5 (USP sterility test: may need brief description of procedure), R (executed batch records). Also, antimicrobial effectiveness testing needs to be evaluated.

I. LABELING					
	Parameter	Yes	No	N/A	Comment
36.	Has the draft package insert been provided?	X	<input type="checkbox"/>	<input type="checkbox"/>	
37.	Have the immediate container and carton labels been provided?	X	<input type="checkbox"/>	<input type="checkbox"/>	Labeling is present (b) (4) this needs to be verified.
38.	Does section contain tradename and established name?	X	<input type="checkbox"/>	<input type="checkbox"/>	(b) (4) RESPIMAT- olodaterol inhalation spray (strength matches free base form)

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J. FILING CONCLUSION					
	Parameter	Yes	No	N/A	Comment
39.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?	X	<input type="checkbox"/>	<input type="checkbox"/>	
40.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.	<input type="checkbox"/>	X	<input type="checkbox"/>	There are no filing issues.
41.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?	X	<input type="checkbox"/>	<input type="checkbox"/>	See earlier in this review under "Overall Product Quality Conclusions and Recommendations"

REVIEW AND APPROVAL

This document will be signed in DARRTS by the following:

CMC Lead or CMC Reviewer
Branch Chief

{See appended electronic signature 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 C SCHROEDER

07/16/2012

Note: CMC comments for 74 day letter are present.

PRASAD PERI

07/17/2012

I concur