CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206756Orig1s000

MICROBIOLOGY / VIROLOGY REVIEW(S)

Product Quality Microbiology Review

26 NOV 2014

NDA: 206-756

Drug Product Name
Proprietary: Stiolto
Non-proprietary: Tiotropium bromide + olodaterol

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
22 MAY 2014	22 MAY 2014	30 MAY 2014	03 JUN 2014
11 AUG 2014	11 AUG 2014	N/A	N/A
14 OCT 2014	14 OCT 2014	N/A	N/A

Applicant/Sponsor
Name: Boehringer Ingelheim Pharmaceuticals, Inc.
Address: 900 Ridgebury Rd.
PO Box 368
Ridgefield, CT 06877
Representative: Anna Wysowskyj
Telephone: 203-798-4280

Name of Reviewer: Jessica G. Cole, PhD

Conclusion: Recommended for Approval

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Original 505(b)(1) NDA

2. SUBMISSION PROVIDES FOR: New drug product for inhalation

3. MANUFACTURING SITE:
Boehringer Ingelheim Pharma GmbH & Co. KG (Ingelheim)
Binger Straße 173
Ingelheim am Rhein
Germany 55216
FEI 3002806556

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:

- Respimat® Inhalation Spray
- 2.5 µg tiotropium bromide/2.5 µg olodaterol per actuation
- Once daily inhalation
- (b) (4) formulation

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: Bronchodilator for patients with COPD

B. SUPPORTING/RELATED DOCUMENTS: Microbiology review of DMF (b) (4) dated 07 February 2013. Microbiology review of NDA 203-108 dated 07 February 2013.

C. REMARKS: This submission is in the eCTD format. The following information request was sent in the 74-day letter and a response was received on 11 August 2014.

1. Provide the sterility test method verification studies to support the proposed formulations.

The following information request was sent to the applicant on 01 October 2014 and a response was received on 14 October 2014.

Microbiology Comment:

Please provide the following information or a reference to its location in the subject submission.

1. We refer to the media fill summary provided in Module 3.2.P.3.5 Section 10. Please provide the following information for the 2013 and any 2014 media fills.
    a. Provide the number of units filled, the number of units rejected (with a brief reason for the rejection), the number of units (b) (4) and the number of positive units.
    b. Indicate whether any visual inspection of media fill units occurs prior to (b) (4) We note a (b) (4) occurs for commercial product.
    c. Provide a more detailed description of the incomplete nature of the April 2013 media fill

and the role of the June 2013 media fill with respect to the erroneously rejected integral units. Describe the April investigation and any corrective actions.

2. We refer to the sterility test verification studies conducted by (b) (4) described in document q00218284-01. Indicate which drug product batches were utilized in these verification studies.

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Executive Summary

I. Recommendations

A. Recommendation on Approvability - Recommended for Approval.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – Not applicable.

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – This (b) (4) sterile solution for inhalation is an (b) (4) drug product.

B. Brief Description of Microbiology Deficiencies – Not applicable.

C. Contains Potential Precedent Decision(s)- ☐ **Yes** ☒ **No**

III. Product Quality Microbiology Risk Assessment

A. Initial Product Quality Microbiology Risk Assessment

CQA	Risk Factor	Prob. of Occ. (O)	Modifier for O[3]	Severity of Effect (S)	Detect. (D)	Risk Priority Number[6] (RPN)	Additional Review Emphasis based on Risk (in addition to normal review process)
Ster.	(b) (4)	9	-1	5	5	200	(b) (4)

(b) (4)

3 = Anti-Microbial Formulation (e.g., meets USP <51>), modifies O (-1) [less emphasis on in process hold times]

6 = RPN = O (after modification when applicable)×S×D

RPN <50 = Low Risk; RPN 50-120 = Moderate Risk; RPN >120 = High Risk

B. Final Risk Assessment – This drug product has been demonstrated to be adequately (b) (4) and is manufactured in a (b) (4) manufacturing environment. The applicant provided adequate validation data to demonstrate the manufacturing process is capable of producing a sterile drug product.

IV. Administrative

A. Reviewer's Signature Jessica Cole, PhD

B. Endorsement Block Bryan Riley, PhD Microbiology Team Lead

Product Quality Microbiology Assessment

Reviewer Comment: The applicant states that the manufacturing process and equipment for this NDA are (b) (4)

1. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 3.2: BODY OF DATA

P DRUG PRODUCT

P.1 Description of the Composition of the Drug Product

- **Description of drug product** – Sterile aqueous multi dose solution for inhalation packaged in a plastic cartridge and delivered with the Respimat inhaler device. Each actuation delivers 2.5 µg tiotropium and 2.5 µg olodaterol and each dose is two actuations. This NDA also contains a description of a 1.25 µg tiotropium and 2.5 µg olodaterol drug product but as the lower strength is not proposed for commercialization this review will only cover the 2.5/2.5 µg product.
- **Drug product composition** –

Table 1- Composition of the drug product (Sponsor Table 1 Module 3.2.P.1)

Name of ingredient	Per actua-tion [mg] [4)]	Percentage formula [g/100ml]	Per cartridge 4.5 ml [5)] [mg]	Function	Reference to standards
Tiotropium bromide monohydrate (corresponds to Tiotropium [1)])	0.003124 (0.0025)	(b) (4)		Drug substance	Company standard
Olodaterol hydrochloride (corresponds to Olodaterol[2)])	0.002736 (0.0025)			Drug substance	Company standard
Benzalkonium chloride (b) (4) (corresponds to benzalkonium chloride)				(b) (4)	NF
Edetate disodium					USP
(b) (4) Hydrochloric acid					Company Standard
Water for injection (WFI)					USP
Total mass	(b) (4)	100.0	(b) (4)	-	-

(b) (4)

1) 1 g tiotropium corresponds to 1.2494 g tiotropium bromide monohydrate.
2) 1 g olodaterol corresponds to 1.0945 g olodaterol hydrochloride
3) (b) (4)
4) One dose consists of two actuations.
5) This quantitative composition statement refers to a nominal filling volume of (b) (4) per cartridge.
(b) (4)

- **Description of container closure system** – The primary container closure system is a plastic reservoir placed into a plastic cartridge with a plastic cap that fits into the Respimat inhaler device.

Figure 1- Container closure system (Sponsor Figure 1 Module 3.2.P.7)

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

- **Container-Closure and Package integrity** – Package integrity was evaluated for the filled reservoirs and for the cartridges that contained filled reservoirs. The proposed test method is (b) (4)

(b) (4)

[redacted]

ADEQUATE

REVIEWER COMMENT – The container closure integrity test (b) (4) [redacted] adequate to support this multiple dose product. The NDA contains the results from a single batch of drug product evaluated for antimicrobial effectiveness and traditionally 3 batches are evaluated. (b) (4)

(b) (4)

[redacted]

P.3 Manufacture

P.3.1 Manufacturers

Boehringer Ingelheim Pharma GmbH & Co. KG
Binger Straße 173
55216 Ingelheim am Rhein, Germany
FEI: 3002806556
DUNS: 551147440

P.3.3 Description of the Manufacturing Process and Process Controls

The applicant states that the process, facilities, personnel and material flow, and all equipment are (b) (4)

(b) (4)

ADEQUATE

REVIEWER COMMENT – The manufacturing process and controls were adequately described for this (b) (4) sterile drug product.

P.3.5 Process Validation and/or Evaluation

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(b) (4)

ADEQUATE

REVIEWER COMMENT – The applicant has conducted process validation studies that demonstrate the proposed manufacturing process is adequate for this sterile drug product.

P.5 Control of Drug Product

P.5.1 Specifications Sterile with (b) (4)

P.5.2 Analytical Procedures

- **Endotoxin** – Not applicable for this inhalation drug product.
- **Sterility** – Current USP<71> testing will occur at (b) (4) and (b) (4)

Information Request dated 04 August 2014

Provide the sterility test method verification studies to support the proposed formulations.

Summary of Response dated 11 August 2014

(b) (4)

(b) (4)

Information request dated 01 October 2014

We refer to the sterility test verification studies conducted by (b) (4) described in document q00218284-01. Indicate which drug product batches were utilized in these verification studies.

Summary of response dated 14 October 2014

Batch (B092000039) was utilized in the sterility test verification studies and this corresponds to Phase III batch 903282.

- **Microbial Limits** – Not applicable.

ADEQUATE

REVIEWER COMMENT – The proposed sterility test method is compendial and was verified to be appropriate for use.

P.7 Container Closure System See section P.1.

P.8 Stability

P.8.1 Stability Summary and Conclusion

MAINTENANCE OF MICROBIOLOGICAL CONTROL AND QUALITY: STABILITY CONSIDERATIONS

(b) (4)

- **Endotoxin** – Not applicable.
- **Microbial Limits** – Not applicable.

P.8.3 Stability Data

All stability data relevant to microbiology were acceptable. The in-use stability data from 5 cartridges per batch are shown in Table 5. The applicant states that because the inhaler is non-sterile the sterility test was not conducted during in-use tests. Table 6 demonstrates that the AET results on 20 pooled cartridges at the end of the 3 month in-use period were adequate.

Table 5- Microbial quality of in-use cartridges (Sponsor Table 12 Module 3.2.P.8.3 U13-2604-01)

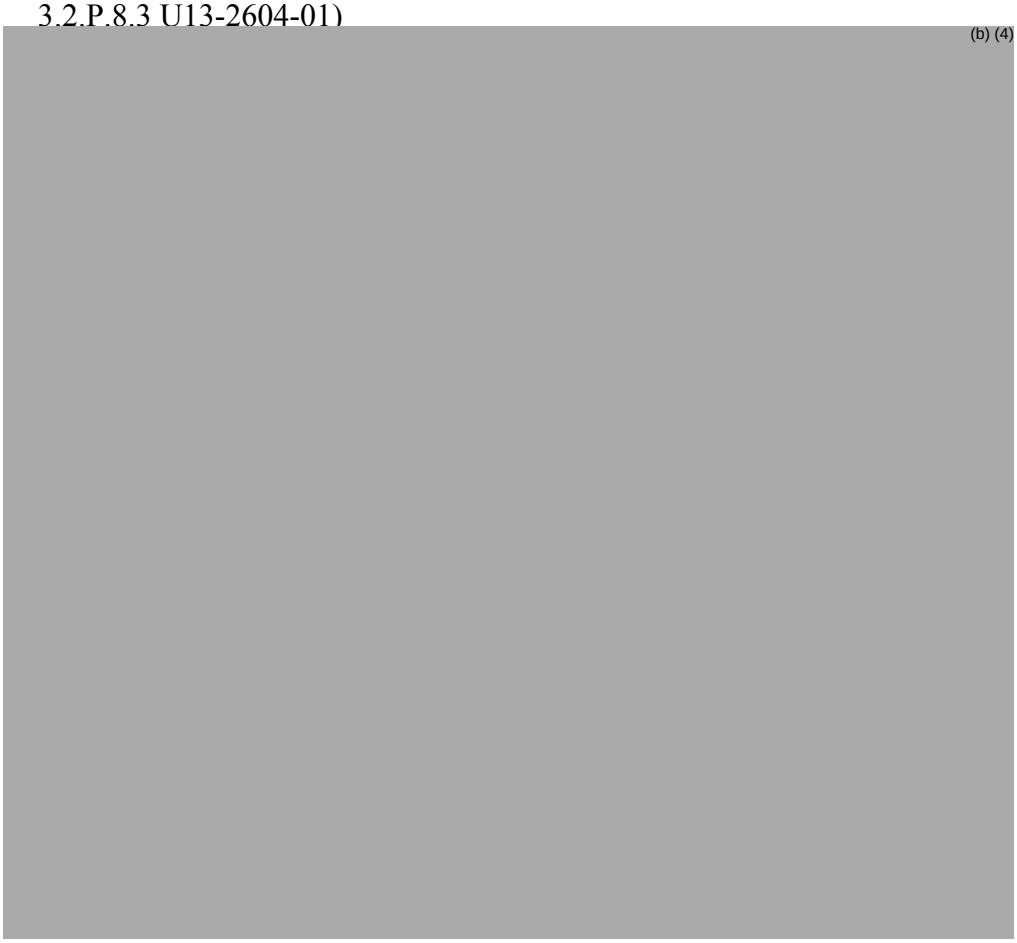

Table 6- Antimicrobial effectiveness testing for in-use cartridges (Sponsor Table 13 Module 3.2.P.8.3 U13-2604-01)

(b) (4)

ADEQUATE

REVIEWER COMMENT – The stability plan and data are adequate to support approval of this NDA.

A APPENDICES - Not applicable.

R REGIONAL INFORMATION

R.1 Executed Batch Record – Executed batch records were provided.

2. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 1

A. PACKAGE INSERT – Not applicable for this (b) (4) drug product.

3. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS:

None.

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/s/

JESSICA COLE
12/03/2014

BRYAN S RILEY
12/03/2014
I concur.

PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

NDA Number: 206-756 **Applicant:** Boehringer Ingelheim Pharmaceuticals **Letter Date:** 22 May 2014

Drug Name: Stiolto (tiotropium bromide with olodaterol) **NDA Type:** 505(b)(1) **Stamp Date:** 22 May 2014

The following are necessary to initiate a review of the NDA application:

	Content Parameter	Yes	No	Comments
1	Is the product quality microbiology information described in the NDA and organized in a manner to allow substantive review to begin? Is it legible, indexed, and/or paginated adequately?	X		
2	Has the applicant submitted an overall description of the manufacturing processes and microbiological controls used in the manufacture of the drug product?	X		
3	Has the applicant submitted protocols and results of validation studies concerning microbiological control processes used in the manufacture of the drug product?	X		
4	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?		X	
5	Has the applicant submitted preservative effectiveness studies (if applicable) and container-closure integrity studies?	X		
6	Has the applicant submitted microbiological specifications for the drug product and a description of the test methods?	X		
7	Has the applicant submitted the results of analytical method verification studies?		X	Need sterility test method verification studies
8	Has the applicant submitted all special/critical studies/data requested during pre-submission meetings and/or discussions?			Not applicable.
9	If sterile, are extended post-constitution and/or post-dilution hold times in the draft labeling supported by microbiological data?			Not applicable.
10	Is this NDA fileable? If not, then describe why.	X		

Additional Comments: This (b) (4) sterile drug product solution for inhalation is to be utilized with the Respimat Inhalation device. (b) (4) is described in DMF (b) (4) and a letter of authorization dated 04 June 2012 was provided.

Comment to include in the 74-day letter:

1. Provide the sterility test method verification studies to support the proposed formulations.

Jessica Cole	24 June 2014
Reviewing Microbiologist	Date
Microbiology Secondary Reviewer/Team Leader	Date

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

/s/

JESSICA COLE
07/08/2014

BRYAN S RILEY
07/08/2014
I concur.