CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021936Orig1s000

MICROBIOLOGY/VIROLOGY REVIEW(S)

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

DATE: 20 August 2014

TO: Jessica L. Lee
Regulatory Health Project Manager
CDER/ODEIII/DPARP

Cc: Eugenia M. Nashed, Chemist
CDER/OPS/ONDQAIII/BRVIII

FROM: Robert J. Mello, Ph.D.
Senior Review Microbiologist
CDER/OPS/New Drug Microbiology Staff

THROUGH: Neal J. Sweeney, Ph.D.
Senior Review Microbiologist
CDER/OPS/New Drug Microbiology Staff

SUBJECT: **NDA 21-936** Class 2 Resubmission
Submission/Received Date: 24 March 2014
Drug Product: SPIRIVA® RESPIMAT® (tiotropium bromide) Inhalation Spray
Sponsor: Boehringer Ingelheim Pharmaceuticals, Inc.

Supporting Documents:

- NDA 21-936, Product Quality Microbiology Review #, A. Lolas (DARRTS date 03July 2008) (Approvable recommendation).
- NDA 21-936, Product Quality Microbiology Review #2, A. Lolas (DARRTS date 14 August 2008) (Approve recommendation).
- Product Quality Microbiology Review #1 of DMF (b) (4), Type III DMF, *Container Closure for Respimat Aqueous Solutions, Boehringer Ingelheim Pharmaceuticals, Inc.*, (J. Cole, DARRTS date 07 February 2013; "Adequate" recommendation).
- NDA 203-108, Product Quality Microbiology Review #1, J. Cole (DARRTS date 07 February 2013) (Approve recommendation).

Microbiology Reviewer Comments: The initial NDA was submitted as a 505(b)(1) on 16 November 2007. The Applicant, Boehringer Ingelheim Pharmaceuticals Inc. (BIPI), received a Complete Response Letter dated 16 September 2008 based on two clinical deficiencies. There were no CMC deficiencies to be addressed in the resubmission. The original application was reviewed and recommended for approval by Product Quality Microbiology on 14 August 2008 (see supporting documents, above). In addition to addressing the items in the CR Letter, the Applicant has updated Modules 1-5 in this submission. Module 3 is a complete replacement of the CMC documentation as well as an update to Module 2, Section 2.3, Quality Overall Summary. The current submission now includes a Letter of Authorization for review of the new Type III DMF (b) (4). The information in that DMF, (b) (4), was part of the original NDA submission reviewed by A. Lolas in 2008. Since then, the Applicant has transferred all of that

information to DMF (b) (4). That DMF, including the most recent Amendment #2, was reviewed in 2013 by J. Cole and found to be "adequate."

As stated above, there were no CMC deficiencies to be addressed in the resubmission. However, there have been changes in the CMC information for both drug substance and drug product.

- *New route of synthesis for tiotropium bromide drug substance.* This had no impact on the microbiology portion of the submission.
- *Two market presentations (sizes), i.e., 14 dose and 30 dose (1 dose = 2 actuations).* The original submission had only the 30 dose marketed presentation. Another, 14 dose presentation has been added (for hospital/institutional administration). This has no impact on the microbiology portion of the submission since the difference between the presentations is only in the set up for the locking mechanism of the inhaler.
- (b) (4) All other formulation items are identical. Therefore, there is no impact on the data covering (b) (4) processing, preservative effectiveness or sterility testing. The (b) (4) formulation is more of a worst case challenge to the sterility test method that has been previously reviewed.
- *New Type III DMFs for the RESPIMAT Inhaler and Container Closure System.* Information on the container closure system has been re-organized in two new Type III DMFs, (b) (4) . DMF (b) (4) has no relevant microbiology information to review. DMF (b) (4) is relevant and has been previously review and found to be adequate (J. Cole, DARRTS date 07 February 2013).
- *Shelf life for drug product extended* (b) (4) *to 36 months.* Within the additional data, the following, microbiology related, conclusions were stated
    - *No relevant changes in benzalkonium chloride levels were observed after 36 months at 25°C / 60 % RH or after 6 months at 40°C / 75 % RH.* Therefore, there is no impact on the preservative effectiveness study results.
    - *No relevant changes in disodium edetate levels were observed after 36 months at*
    - *25°C / 60 % RH or after 6 months at 40°C / 75 % RH.* Again, there is no impact on the preservative effectiveness study results.
    - *The solution remained sterile after 36 months at 25°C / 60 % RH.* There is no impact on the sterility assurance over the additional time in storage.
    - *Sterile Process validation:* (b) (4) Processes and data were updated. Review of the documentation indicates no material changes affecting the sterility assurance of the product (b) (4) . "Results of Media Fills", [Table 13] was updated to show results of media fill runs performed from 2007 through 2012. With the exception of a failure in late 2008 (properly investigated and with CAPAs implemented) the subsequent MF trials ranged from (b) (4) units per trial. These all passed the acceptance criteria (aligned with the 2004 (b) (4) guidance). Updates were provided for the environmental monitoring program to provide more detail and to be aligned with ISO 14644-1 and the 2004 (b) (4) guidance.

CONCLUSION:

Overall, the information submitted was either consistent with or an improvement to the information previously reviewed, and is therefore, **ACCEPTABLE**.

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/s/

ROBERT J MELLO
08/22/2014

NEAL J SWEENEY
08/22/2014
I concur.

Product Quality Microbiology Review

14 AUG 2008

NDA: 21-936 N-000 BC

Drug Product Name
Proprietary: Spiriva® Respimat®
Non-proprietary: Tiotropium bromide inhalation spray
Drug Product Priority Classification: S

Review Number: 2

Dates of Submission(s) Covered by this Review

Letter	Stamp	Review Request	Assigned to Reviewer
24-JUL-2008	25-JUL-2008	N/A	25-JUL-2008

Submission History (for amendments only)

Submission Date(s)	Microbiology Review #	Review Date(s)
16-NOV-2007	1	02-JUL-2008

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

Representative: Walter J. Robak Jr.
Sr. Associate Director, CMC Regulatory Affairs
Telephone: 203-798-9958

Name of Reviewer: Anastasia G. Lolas

Conclusion: Recommended for approval

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: BC amendment to new drug application

2. SUBMISSION PROVIDES FOR: Response to microbiology questions sent on 08-JUL-2008

3. MANUFACTURING SITE:
Boehringer Ingelheim Pharma GmbH & Co. KG
Binger Strasse 173
55216 Ingelheim am Rhein
Germany

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:
- Sterile aqueous multiple-dose solution in a cartridge (4 g) for use with a Respimat® inhaler
- Oral inhalation
- 5 µg (2 inhalations of 2.5 µg each), 30 doses (60 metered actuations)/cartridge

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

6. PHARMACOLOGICAL CATEGORY: Treatment of bronchospasm associated with chronic pulmonary disease including chronic bronchitis and emphysema

B. SUPPORTING/RELATED DOCUMENTS:
- Microbiology Review #1 of NDA 21-936 dated 02-JUL-2008

C. REMARKS: The BC amendment was submitted in paper. The first microbiology review identified 9 questions to be sent to the applicant. An electronic communication was sent on 08-JUL-2008. An electronic response was received on 25-JUL-2008.

file name: N021936R2.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability – NDA 21-936 is recommended for approval based on product quality microbiology

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – Spiriva® Respimat® is a sterile aqueous solution for inhalation packaged in an inhaler. The inhaler is a novel, pocket-sized, propellant-free device. The product is contained in a cartridge. The product quality microbiology is reviewed including the sterility of the final product and preservative effectiveness following the insertion of the cartridge into the inhaler. In this review, the responses to the microbiology questions identified in the first review are evaluated.

B. Brief Description of Microbiology Deficiencies – None

C. Assessment of Risk Due to Microbiology Deficiencies – N/A

III. Administrative

A. Reviewer's Signature _____
Anastasia G. Lolas

B. Endorsement Block
James L. McVey, Microbiology Team Leader

C. CC Block
N/A

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/s/

Anastasia Lolas
8/14/2008 02:28:13 PM
MICROBIOLOGIST

James McVey
8/14/2008 02:35:51 PM
MICROBIOLOGIST
I concur.

Product Quality Microbiology Review

02 JUL 2008

NDA: 21-936

Drug Product Name
Proprietary: Spiriva® Respimat®
Non-proprietary: Tiotropium bromide inhalation spray
Drug Product Priority Classification: S

Review Number: 1

Dates of Submission(s) Covered by this Review

Letter	Stamp	Review Request	Assigned to Reviewer
16-NOV-2007	16-NOV-2007	06-FEB-2008	14-FEB-2008

Submission History (for amendments only) – N/A

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

Representative: Jeffrey R. Snyder
Executive Director, Drug Regulatory Affairs
Telephone: 203-778-7727
E-mail: jsnyder@rdg.boerhinger-ingelheim.com

Name of Reviewer: Anastasia G. Lolas

Conclusion: Approvable pending the resolution of product quality microbiology deficiencies (see Section 3 of review)

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: New drug application

2. SUBMISSION PROVIDES FOR: New inhalation spray drug product

3. MANUFACTURING SITE:
Boehringer Ingelheim Pharma GmbH & Co. KG
Binger Strasse 173
55216 Ingelheim am Rhein
Germany

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:
- Sterile aqueous multiple-dose solution in a cartridge (4 g) and a Respimat® inhaler
- Oral inhalation
- 5 µg (2 inhalations of 2.5 µg each), 30 doses (60 metered actuations)/cartridge

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

6. PHARMACOLOGICAL CATEGORY: Treatment of bronchospasm associated with chronic pulmonary disease including chronic bronchitis and emphysema

B. SUPPORTING/RELATED DOCUMENTS:
- INDs 65,127 and 46,687
- NDA 21-395; the same drug substance is being used in the approved Spiriva® Handihaler® (titropium bromide inhalation powder),

C. REMARKS: This is a hybrid paper and electronic submission in CTD format. Module 2 is electronic while Module 3 is not. Module 3 jackets were borrowed from the Review Chemist. Several DMFs are referenced for the drug substance and the materials used for the inhaler. The Initial Quality Assessment states that the sterility assurance of the unopened cartridge and the preservative effectiveness test are critical issues that need to be evaluated.

file name: N021936R1.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability – NDA 21-936 is approvable pending the resolution of product quality microbiology deficiencies (see Section 3)

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – Spiriva® Respimat® is a sterile aqueous solution for inhalation packaged in an inhaler. The inhaler is a novel, pocket-sized, propellant-free device. The product is contained in a cartridge. The product quality microbiology is reviewed including the sterility of the final product and preservative effectiveness following the insertion of the cartridge into the inhaler.

B. Brief Description of Microbiology Deficiencies – Additional information is needed regarding the antimicrobial effectiveness test, sterilization processes and media fills. A data summary of a bacteriostasis/fungistasis study is not provided.

C. Assessment of Risk Due to Microbiology Deficiencies – Moderate risk to the patient.

III. Administrative

A. Reviewer's Signature _____
Anastasia G. Lolas

B. Endorsement Block
Bryan S. Riley, Ph.D.

C. CC Block
N/A

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/s/

Anastasia Lolas
7/2/2008 05:14:03 PM
MICROBIOLOGIST

Bryan Riley
7/3/2008 06:51:02 AM
MICROBIOLOGIST
I concur.