Product Quality Microbiology Review

28 SEP 2010

NDA: 200-678

Drug Product Name
Proprietary: (proposed)
Non-proprietary: Saxagliptin/metformin HCl extended-release

Review Number: 1

Dates of Submission(s) Covered by this Review

<table>
<thead>
<tr>
<th>Submit</th>
<th>Received</th>
<th>Review Request</th>
<th>Assigned to Reviewer</th>
</tr>
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<tbody>
<tr>
<td>29 DEC 2009</td>
<td>29 DEC 2009</td>
<td>2 FEB 2010</td>
<td>17 FEB 2010</td>
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<tr>
<td>23 APR 2010</td>
<td>23 APR 2010</td>
<td>N/A</td>
<td>N/A</td>
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<td>24 SEP 2010</td>
<td>24 SEP 2010</td>
<td>N/A</td>
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</tbody>
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Applicant/Sponsor
Name: Bristol-Myers Squibb Co.
Address: P.O. Box 4000
Princeton, NJ 08543-4000
Representative: Pamela J. Smith, M.D.
Telephone: 609-252-5228

Name of Reviewer: Jessica G. Cole

Conclusion: Recommend approval.
Product Quality Microbiology Data Sheet

A. 1. **TYPE OF SUBMISSION:** Original NDA

2. **SUBMISSION PROVIDES FOR:** New fixed-dose combination product.

3. **MANUFACTURING SITE:** Bristol-Myers Squibb
   4601 Highway 62 East
   Mount Vernon, IN 47620 USA

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**
   - Oral tablet
   - 5/500 mg, 5/1000 mg, 2.5/1000 mg saxagliptin/metformin HCL-XR

5. **METHOD(S) OF STERILIZATION:** oral tablet.

6. **PHARMACOLOGICAL CATEGORY:** Indicated for Type 2 diabetes treatment.

B. **SUPPORTING/RELATED DOCUMENTS:** None.

C. **REMARKS:**
The following microbiology information request was included in the 74-day letter to the applicant.

**Reviewer Comment**
Please provide the following information:
1. The in the finished drug product.
2. The microbial limits test validation studies or a summary of these studies.
3. The microbial limits testing protocols 5450A, 249965, 249966, and 249967.
4. A justification for only performing microbial limits testing during routine production.

A response was received 23 April 2010 and the information was incorporated into the relevant sections of this review.

A second comment was sent to the sponsor through the project manager on 7/7/10:

**Reviewer Comment**

- Microbial limits data for critical raw materials,
- Microbiological environmental monitoring data for critical processing steps that can be related to the batch, and
- In-process control parameters that may affect product quality microbiology.

In addition, microbial limits testing should be performed at the initial time point (at a minimum) on stability samples.

A response was received on 24 September and the response was incorporated into the relevant sections of this review.

filename: N200678R1.doc
Executive Summary

I. Recommendations

A. Recommendation on Approvability – Recommended for approval on the basis of product quality microbiology.

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 – The drug product is a [redacted] tablet manufactured [redacted]

B. Brief Description of Microbiology Deficiencies – Not applicable.

C. Assessment of Risk Due to Microbiology Deficiencies – Not applicable.

III. Administrative

A. Reviewer's Signature _____________________________ Jessica G. Cole, Ph.D.

B. Endorsement Block _____________________________ Stephen Langille, Ph.D.
   Senior Microbiology Reviewer

C. CC Block
   N/A

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/s/

JESSICA COLE
09/29/2010

STEPHEN E LANGILLE
09/29/2010
## PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

**NDA Number:** 200678  
**Applicant:** Bristol-Myers Squibb  
**Letter Date:** 12/29/2009  
**Drug Name:** Saxagliptin/Metformin XR  
**NDA Type:** Standard  
**Stamp Date:** 12/29/2009

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

<table>
<thead>
<tr>
<th>Content Parameter</th>
<th>Yes</th>
<th>No</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>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?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Has the applicant submitted an overall description of the manufacturing processes and microbiological controls used in the manufacture of the drug product?</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>3. Has the applicant submitted protocols and results of validation studies concerning microbiological control processes used in the manufacture of the drug product?</td>
<td>X</td>
<td></td>
<td>Protocols for microbial limits testing not provided.</td>
</tr>
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<td>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?</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>5. Has the applicant submitted preservative effectiveness studies (if applicable) and container-closure integrity studies?</td>
<td>X</td>
<td></td>
<td>Not applicable</td>
</tr>
<tr>
<td>6. Has the applicant submitted microbiological specifications for the drug product and a description of the test methods?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Has the applicant submitted the results of analytical method verification studies?</td>
<td>X</td>
<td></td>
<td>No information is provided on the verification studies for microbial limits testing.</td>
</tr>
<tr>
<td>8. Has the applicant submitted all special/critical studies/data requested during pre-submission meetings and/or discussions?</td>
<td>X</td>
<td></td>
<td>Not applicable.</td>
</tr>
<tr>
<td>9. Is this NDA fileable? If not, then describe why.</td>
<td>X</td>
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**Additional Comments:** Please provide the protocols (5450A, 249965, 249966, and 249967) and the validation studies for the microbial limits tests.

2/3/2010  
Jessica G. Cole, Ph.D. Date  
Bryan S. Riley, Ph.D. Senior Review Microbiologist Date
<table>
<thead>
<tr>
<th>Application Type/Number</th>
<th>Submission Type/Number</th>
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<th>Product Name</th>
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<tr>
<td>NDA-200678</td>
<td>ORIG-1</td>
<td>BRISTOL MYERS SQUIBB</td>
<td>(saxagliptin + metformin XR) Tablets</td>
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/s/

JESSICA COLE
02/03/2010

BRYAN S RILEY
02/03/2010
I concur.