

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**200678Orig1s000**

**MICROBIOLOGY REVIEW(S)**

# Product Quality Microbiology Review

28 SEP 2010

**NDA:** 200-678

**Drug Product Name**

**Proprietary:** (b) (4) (proposed)

**Non-proprietary:** Saxagliptin/metformin HCl extended-release

**Review Number:** 1

## **Dates of Submission(s) Covered by this Review**

<b>Submit</b>	<b>Received</b>	<b>Review Request</b>	<b>Assigned to Reviewer</b>
29 DEC 2009	29 DEC 2009	2 FEB 2010	17 FEB 2010
23 APR 2010	23 APR 2010	N/A	N/A
24 SEP 2010	24 SEP 2010	N/A	N/A

## **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:** (b) (4) 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 (b) (4) 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 (b) (4) 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**

(b) (4)

(b) (4)

. The product specification should state that the product will meet the requirements of USP<1111>, if tested. These process controls, tests and acceptance criteria should be identified in the batch release criteria, and include, for example:

- 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 (b) (4) 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.

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## **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 (b) (4) tablet manufactured (b) (4)
- 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/

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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:

	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	Protocols for microbial limits testing not provided.
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	Not applicable (b) (4)
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	No information is provided on the verification studies for microbial limits testing.
8	Has the applicant submitted all special/critical studies/data requested during pre-submission meetings and/or discussions?			Not applicable.
9	Is this NDA fileable? If not, then describe why.	X		

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

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-200678

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ORIG-1

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BRISTOL MYERS  
SQUIBB

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 (b) (4) (saxagliptin +  
metformin XR) Tablets

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JESSICA COLE  
02/03/2010

BRYAN S RILEY  
02/03/2010  
I concur.