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RESEARCH**

APPLICATION NUMBER:
202293Orig1s000

MICROBIOLOGY/VIROLOGY REVIEW(S)

Product Quality Microbiology Review

31-AUG-2011

NDA 202-293/N-000

Drug Product Name

Proprietary: (b) (4)

Non-proprietary: Dapagliflozin

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
17-AUG-2011	17-AUG-2011	N/A	N/A
27-DEC-2010	28-DEC-2010	04-JAN-2011	06-JAN-2011

Applicant/Sponsor

Name: Bristol-Myers Squibb (BMS)

Address: P.O. Box 5100
Wallingford, CT 06492-7660

Representative: Amy Jennings, Ph.D.
Director, US/Global Regulatory Lead-Dapagliflozin

Telephone: 203-677-3821

Name of Reviewer: Steven Fong, Ph.D.

Conclusion: CMC-Microbiology Recommends APPROVE.

Product Quality Microbiology Data Sheet

- A. 1. **TYPE OF SUBMISSION:** Original NDA
2. **SUBMISSION PROVIDES FOR:** New drug product
3. **MANUFACTURING SITE:** The drug product will be manufactured at two different facilities:
- BMS
State Road #3, Km 77.5
Humacao, Puerto Rico 00791
- BMS
4601 Highway 62 East
Mount Vernon, Indiana 47620
4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**
- Non-sterile, solid oral dose, film-coated tablets.
 - 5 or 10 mg dapagliflozin drug substance per tablet.
5. **METHOD(S) OF STERILIZATION:** N/A. Product is non-sterile.
6. **PHARMACOLOGICAL CATEGORY:** Type 2 diabetes therapeutic.

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

C. **REMARKS:**

- 1) The NDA was submitted electronically in CTD format.
- 2) Clinical trials for dapagliflozin were conducted under IND 68,652 (submitted 20-NOV-2003).
- 3) On 11-JAN-2007, BMS formed an alliance with AstraZeneca to develop dapagliflozin as a diabetes treatment. BMS continues to hold IND 68,652, and filed the subject NDA in behalf of the alliance.
- 4) On 01-AUG-2011 the following IR was submitted to BMS:

Your drug product manufacturing protocol does not include procedures for controlling microbiological quality, and your drug product Specification does not include a microbial limits acceptance criterion. Although the observation (Section 3.2.P.2.5) that dapagliflozin film-coated tablets (b)(4) is supportive of microbiological quality, it is not in itself sufficient to justify exclusion of a microbial limits criterion. In order to omit finished product microbial limits testing as a release requirement, you should implement manufacturing controls, tests, and

acceptance criteria that provide assurance of the microbiological quality for each batch of product, and provide an amendment documenting the procedures that will be performed to achieve this goal. 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 [REDACTED] (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.

In lieu of modifying your manufacturing procedure as noted above, the drug product specification should be modified to include a microbial limits acceptance criterion.

An Amendment response, Supporting Document 41, was received 17-AUG-2011.

filename: N202293r1.doc

Executive Summary

I. Recommendations

- A. Recommendation on Approvability** - Recommended for approval from a microbiology quality standpoint.
- B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable** – None.

II. Summary of Microbiology Assessments

- A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology** – (b) (4)



The product Specification includes a microbial limits acceptance criterion.

- B. Brief Description of Microbiology Deficiencies** – None.
- C. Assessment of Risk Due to Microbiology Deficiencies** – N/A

III. Administrative

- A. Reviewer's Signature** _____
Steven E. Fong, Ph.D.
Microbiology Reviewer
- B. Endorsement Block** _____
John Metcalfe, Ph.D.
Senior Microbiology Reviewer
- C. CC Block**—N/A

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/s/

STEVEN E FONG

08/31/2011

Recommended for approval from a microbiology quality standpoint.

JOHN W METCALFE

08/31/2011

I concur.