CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206111Orig1s000

MICROBIOLOGY / VIROLOGY REVIEW(S)

M E M O R A N D U M

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

DATE: 17 February 2015

TO: NDA 206111

FROM: John W. Metcalfe, Ph.D.
Branch Chief (Acting)
CDER/OPQ/OPF/DMA/Branch IV

THROUGH: Bryan S. Riley, Ph.D.
Branch Chief (Acting)
CDER/OPQ/OPF/DMA/Branch II

cc: Michael G. White
Regulatory Health Project Manager
CDER/OND/ODEII/DMEP

SUBJECT: Product Quality Microbiology assessment of Microbial Limits for empagliflozin/metformin hydrochloride [Submission Dates: 04 August 2014; 14 January 2015; 30 January 2015]

The NDA for empagliflozin/metformin hydrochloride does not include a Microbial Enumeration specification for drug product release or stability; however, the applicant provides a suitable rationale for the exclusion of this testing. Therefore, this submission is recommended for approval from the standpoint of product quality microbiology.

The proposed drug product is a tablet for oral administration.

The applicant presents a rationale for waiving Microbial Limits testing for product release and stability. The rationale and corresponding risk assessment are presented in the 14 January 2015 amendment and includes a discussion of the following:

- Raw material controls
- Environmental monitoring
- Validated equipment (b) (4) holding times
- Microbiological stability (b) (4)
- Confirmatory drug product batch release and stability data

Those raw materials (b) (4) are controlled according to USP/NF monographs for

these components. The applicant considers these particular raw materials to be "Critical Material Attributes". The manufacturing area is monitored for environmental microorganisms on a periodic basis [redacted] Alert and action levels are provided in table 1 of the 14 January 2015 submission.

[redacted] A microbiological challenge study was performed. [redacted] In addition, a microbiological study was performed [redacted] Samples were [redacted] tested for microbial concentration. The data from this study are provided in table 4 of the 14 January 2015 submission (< [redacted] CFU/mL Total Aerobic Microbial Count and < [redacted] CFU/mL Total Yeasts and Molds Count at both sampling time points), and are acceptable. Finally, the applicant has performed [redacted] microbial enumeration studies on stability batches (6 batches total, one each of 6 different product concentrations). [redacted] microbial counts were lower than the suggested limits in USP<1111> for the subject dosage form.

The applicant amended the drug product release and stability specifications to remove microbiological testing (30 January 2015 amendment).

ADEQUATE

Reviewer Comments – The applicant's proposal to waive microbial limits testing for product release and stability is acceptable.

END

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/s/

JOHN W METCALFE
02/17/2015

BRYAN S RILEY
02/17/2015
I concur.

PRODUCT QUALITY MICROBIOLOGY NON-STERILE

DRUG PRODUCT FILING CHECKLIST

NDA Number: 206111 **Applicant:** Boehringer Ingelheim Pharmaceuticals, Inc. **Letter Date:** 04 August 2014

Drug Name: Empagliflozin/metformin hydrochloride **NDA Type:** 505(b)(2) **Stamp Date:** 04 August 2014

Dosage Form: Tablet **Reviewer:** John W. Metcalfe, PhD

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		Modules 3.2.P.1, 3.2.P.2, 3.2.P.5.1, 3.2.P.5.2, 3.2.P.5.3, & 3.2.P.8.
2	Has the applicant submitted an overall description of the manufacturing processes and microbiological controls used in the manufacture of the drug product?	X		Module 3.2.P.3.3.
3	Has the applicant submitted microbiological specifications for the drug product and a description of the test methods?	X		Module Applicant (b) (4) for Mic Limits.
4	Has the applicant submitted the results of analytical method verification studies?	X		Module 3.2.P.5.3.
5	Has the applicant submitted preservative effectiveness studies (if applicable)?			Not applicable to drug product.
6	Is this NDA fileable? If not, then describe why.	X		

Additional Comments: There is a Microbiology Information Request on page 2 of this review.

21 August 2014

John W. Metcalfe, Ph.D. Date
Senior Microbiology Reviewer, CDER/OPS/NDMS

21 August 2014

Bryan S. Riley, Ph.D. Date
Team Leader (Acting), CDER/OPS/NDMS

Microbiology Information Request to be forwarded to Applicant

You propose to perform [redacted] (b) (4) Address the following points.

1. Identify and justify critical control points in the manufacturing process that could affect microbial load of the drug product.

    a. Define [redacted] (b) (4)

    b. Define [redacted] (b) (4)

2. Describe microbiological monitoring and acceptance criteria for the critical control points that you have identified. Verify the suitability of your testing methods for your drug product. Conformance to the acceptance criteria established for each critical control point should be documented in the batch record in accordance with 21 CFR 211.188.

3. Describe activities taken when microbiological acceptance criteria are not met at control points.

In addition to these points, address the following:

1. You should minimally perform microbial limits testing at the initial stability testing time point. Provide an updated stability schedule to reflect this testing.

If you choose to omit microbial limits testing for release, then remove the microbial limits tests and acceptance criteria from the drug product release specification. Alternatively, you may retain a microbial limits specification for product release, but testing must be performed on every lot of drug product produced.
Please submit a revised drug product release specification for whichever microbial limits testing alternative that you select.

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/s/

JOHN W METCALFE
08/21/2014

BRYAN S RILEY
08/21/2014
I concur.