CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206073Orig1s000

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: 08 August 2014

TO: NDA 206073

FROM: Erika Pfeiler, Ph.D.
Microbiologist
CDER/OPS/NDMS

THROUGH: Stephen Langille, Ph.D.
Senior Review Microbiologist
CDER/OPS/NDMS

cc: Callie Cappel-Lynch
CDER/OND/ODEII/DMEP

SUBJECT: Product Quality Microbiology assessment of Microbial Limits for Empagliflozin and Linagliptin tablets [Submission Date: 29 January 2014]

The NDA for Empagliflozin and Linagliptin tablets presents a waiver for microbial limits testing for product release, and 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 product is a film-coated tablet with 10 mg/5 mg and 25 mg/5 mg (Empagliflozin/Linagliptin) presentations.

The drug product is manufactured (b) (4) The applicant presents a rationale for waiving microbial limits testing for product release and stability. The rationale describes raw material controls, environmental monitoring procedures, equipment holding times, (b) (4) holding times, and (b) (4) holding times are in place to ensure microbiological quality. (b) (4)

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[redacted]

Further, the applicant provides stability data to demonstrate a lack of microbial growth in the finished product. Microbial limits testing was performed for primary stability batches. Specifications for these studies are in agreement with those described in USP <1111>, and include a total aerobic microbial count of NMT [redacted] CFU/g, a total yeast and mold count of NMT [redacted] CFU/g, and the absence of *Escherichia coli* per gram. Testing was performed using methods described in USP <61> [redacted] Microbiological testing [redacted] was performed at initial, 6, 12, and 24 month timepoints under long-term storage conditions (25°C/60% RH) and at initial and 6 months under accelerated conditions (30°C/75% RH). All batches met microbiological acceptance criteria at each time point tested. Under long-term storage conditions, [redacted] in the tablets remained below [redacted]. [redacted] under accelerated conditions to a maximum of [redacted], with no noted increase in microbial load.

The drug product will be tested for microbial limits annually as part of the post-approval stability protocol.

ADEQUATE

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

END

Filing Letter Information Request

1. *You propose to perform skip lot testing for the Microbial Limits test for drug product release. Skip-lot testing for drug products is not allowed by regulation (21 CFR 211.165 (a) and (b).) If a drug product release specification includes tests and acceptance criteria for a given attribute, then the test must be performed on every batch. However, microbial limits testing may be omitted from the product release specification provided adequate upstream microbiological controls are established and documented. If you wish to omit the microbial limits specification, more information on your process is needed. Address the following points.*
    a. *Identify and justify critical control points in the manufacturing process that could affect microbial load of the drug product.*
        i. [redacted]
        ii.
    b. *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.*
    c. *Describe activities taken when microbiological acceptance criteria are not met at control points.*

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.

2. *Your release and stability specifications include microbial limits and the absence of Escherichia coli, but you do not describe testing methods. Describe these methods and state whether validation has been performed to ensure that these methods are adequate for use with the drug product.*

30 June 2014 Response
The applicant provided a rationale for omitting microbial limits testing for product release. The applicant plans to submit revised release specifications at a later date.

31 July 2014 Response
The applicant provided a revised release specification, omitting microbial limits testing.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ERIKA A PFEILER
08/08/2014

STEPHEN E LANGILLE
08/08/2014

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