

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206073Orig1s000

MICROBIOLOGY / VIROLOGY REVIEW(S)

MEMORANDUM

(b) (4)

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 (b) (4) CFU/g, a total yeast and mold count of NMT (b) (4) CFU/g, and the absence of *Escherichia coli* per gram. Testing was performed using methods described in USP <61> (b) (4). Microbiological testing (b) (4) 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, (b) (4) in the tablets remained below (b) (4). (b) (4) under accelerated conditions to a maximum of (b) (4), 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. (b) (4)
 - ii. (b) (4)
 - 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*

MEMORANDUM

- 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.

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/s/

ERIKA A PFEILER
08/08/2014

STEPHEN E LANGILLE
08/08/2014

PRODUCT QUALITY MICROBIOLOGY NON-STERILE

DRUG PRODUCT FILING CHECKLIST

NDA Number: 206073 **Applicant:** Boehringer Ingelheim Pharmaceuticals, Inc. **Letter Date:** 29 January 2014

Drug Name: Empagliflozin/Linagliptin **NDA Type:** 505(b)(1) **Stamp Date:** 30 January 2014
Glyxambi[®] (proposed)

Dosage Form: Tablet **Reviewer:** Erika Pfeiler, Ph.D.

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 microbiological specifications for the drug product and a description of the test methods?	X		See Additional Comments.
4	Has the applicant submitted the results of analytical method verification studies?		X	See Additional Comments.
5	Has the applicant submitted preservative effectiveness studies (if applicable)?			N/A
6	Is this NDA fileable? If not, then describe why.	X		

Additional Comments: The application contains microbial limits release specifications for the two presentations of drug product (25 mg empagliflozin/5 mg linagliptin, 10 mg empagliflozin/5 mg linagliptin). The release specifications are in agreement with those listed in USP <1111> for dosage forms of this type; however, the application states that microbial limits testing will be performed as skip-lot testing with one production batch per year tested. Additionally, the application does not describe test methods for microbial limits testing. Information requests to resolve these issues will be sent to the applicant.

Product Quality Microbiology 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. (b) (4)
 - ii. (b) (4)
- 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.

Erika Pfeiler, Ph.D.
Microbiologist

Date

John Metcalfe, Ph.D.
Senior Review Microbiologist

Date

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/s/

ERIKA A PFEILER
02/25/2014

JOHN W METCALFE
02/25/2014
I concur.