

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**206038Orig1s000**

**MICROBIOLOGY / VIROLOGY REVIEW(S)**

MEMORANDUM



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

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**DATE:** 09 December 2014

**TO:** NDA 206-038

**FROM:** Jessica G. Cole, PhD  
Review Microbiologist  
CDER/OPS/New Drug Microbiology Staff  
(301) 796-5148

**THROUGH:** Bryan Riley, PhD  
Microbiology Team Leader  
CDER/OPS/New Drug Microbiology Staff

**cc:** Leila Hann  
Regulatory Project Manager  
CDER/OND/ODEII/DPARP

**SUBJECT:** Product Quality Microbiology assessment of microbial limits for VX-809 (lumacaftor/ivacaftor) [Pre Submission Date: 30 July 2014]

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**The Microbial Limits specification for VX-809 (lumacaftor/ivacaftor) is acceptable from a Product Quality Microbiology perspective. Therefore, this submission is recommended for approval from the standpoint of product quality microbiology.**

VX-809 (lumacaftor/ivacaftor) is a tablet for oral administration. This NDA describes combination product (b) (4) (200/125 mg (b) (4) tablet. This is an orphan drug product indicated for the treatment of cystic fibrosis and the NDA has a rolling submission and accelerated approval deadlines. (b) (4)

The applicant proposes (b) (4)

The 125 mg ivacaftor tablet (b) (4)

The fixed dose combination products will be manufactured at three proposed drug product sites: (b) (4) Vertex Pharmaceuticals Inc. Boston, MA, (b) (4)

Each site will use a continuous (b) (4) process (b) (4)

The microbial attributes were assessed by the

# MEMORANDUM

(b) (4)

(b) (4)

(b) (4)

The 125 mg ivacaftor tablet and the (b) (4) combination table<sub>b</sub> are tested for microbial limits (b) (4) on stability using a method consistent with USP Chapter <61> (Microbiological Examination of Non-sterile Products: Microbial Enumeration Tests) and <62> (Microbiological Examination of Non-sterile Products: Tests for Specified Microorganisms). The acceptance criteria are consistent with USP Chapter <1111> (Microbiological Examination of Non-sterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use).

The Microbial Limits test methods were verified to be appropriate for use with the drug product following procedures consistent with those in USP Chapter <61> and <62>.

## MEMORANDUM

Information request dated 17 October 2014

You propose to waive microbial limits release testing for your drug product. This proposal may be acceptable provided adequate (b) (4) controls are established and documented. The use of a continuous manufacturing process for the fixed dose combination products should include an understanding of the microbiological risks associated with (b) (4) (b) (4) steps. More information on your process is needed. Address the following points for each of the three proposed manufacturing facilities.



Summary of response dated 14 November 2014



Information request dated 17 October 2014

Conformance to the acceptance criteria established for each critical control point described in question 1 should be documented in the batch record in accordance with 21 CFR 211.188. Describe activities taken when microbiological acceptance criteria are not met at control points.

Summary of response dated 14 November 2014

The applicant commits to including the maximum holding times in the batch record.

Information request dated 17 October 2014

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Provide the microbial specification for incoming components, as applicable.

Summary of response dated 14 November 2014

USP<61> and <62> tests are performed

(b) (4)

The applicant refers to the stability data for supporting information on the microbiological quality for the drug substance

(b) (4)

Information request dated 17 October 2014

Confirm that the USP<61> and <62> methods were verified to be suitable for use with the proposed drug products according to the methods described in the compendia.

Summary of response dated 14 November 2014

Method verification studies were conducted with the proposed drug products.

### ADEQUATE

**Reviewer Comments – The microbiological quality of the drug product is controlled via a suitable (b) (4) control strategy and stability testing protocol. The microbial enumeration data provided in this submission demonstrate a low microbial content in the final drug products.**

**END**

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/s/  
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JESSICA COLE  
12/09/2014

BRYAN S RILEY  
12/11/2014  
I concur.