

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205422Orig1s000**

**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:** 02 December 2014

**TO:** NDA 205422

**FROM:** John W. Metcalfe, Ph.D.  
Senior Review Microbiologist  
CDER/OPS/New Drug Microbiology Staff

**THROUGH:** Bryan S. Riley, Ph.D.  
Team Leader (Acting)  
CDER/OPS/New Drug Microbiology Staff

**cc:** Kofi Ansah  
Senior Project Manager  
CDER/OND/ODEI/DPP

**SUBJECT:** Product Quality Microbiology assessment of Microbial Limits for  
brexpiprazole  
[Submission Dates: 11 July 2014 & 14 October 2014]

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**The Microbial Limits specification for brexpiprazole is acceptable from a Product Quality Microbiology perspective. Therefore, this submission is recommended for approval from the standpoint of product quality microbiology.**

Brexpiprazole is a tablet for oral administration.

The drug product is tested for Microbial Limits at release 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 Microbial Limits 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>.

The drug product will also be tested for Microbial Limits annually as part of the post-approval stability protocol.

## MEMORANDUM

The microbial enumeration tests, limits and methods are provided in table 1.

Table 1. Microbial Enumeration Tests

	<b>Limits</b>	<b>Method</b>
Microbial Enumeration Tests	Total Aerobic Microbial Count: $\leq$ (b) (4) CFU/g Total Yeasts and Molds Count: $\leq$ (b) (4) CFU/g	USP<61>, Pour plate method
Specified Organisms	<i>E. coli</i> : Absent	USP<62>

### ADEQUATE

**Reviewer Comments – The microbiological quality of the drug product is controlled via a suitable testing protocol.**

**END**

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/s/  
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JOHN W METCALFE  
12/02/2014

BRYAN S RILEY  
12/02/2014  
I concur.



## Microbiology Information Request to Forward to Applicant

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.

1. Identify and justify critical control points in the manufacturing process that could affect microbial load of the drug product.
  - a.  (b) (4)
  - b. 
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.

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/  
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JOHN W METCALFE  
08/08/2014

BRYAN S RILEY  
08/08/2014  
I concur.