

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206143Orig1s000

MICROBIOLOGY / VIROLOGY REVIEW(S)

MEMORANDUM



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

DATE: 6 June 2014

TO: NDA 206143

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

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

cc: Alexis T. Childers
Senior Regulatory Health Project Manager
OND/DCRP

SUBJECT: Product Quality Microbiology assessment of Microbial Limits for Ivabradine Tablets (5 mg and 7.5 mg) [Submission Date for CMC Module: 30 April 2014]

The Microbial Limits specification for Ivabradine (Immediate Release Tablet) is acceptable from a Product Quality Microbiology perspective. Therefore, this submission is recommended for approval from the standpoint of product quality microbiology.

Ivabradine 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).

MEMORANDUM

Table 1 – Microbial Limits Specifications

Test	Acceptance Criteria
Total Aerobic Microbial Count (USP <61>)	NMT (b) (4) CFU/g
Total Yeast and Mold Count (USP <61>)	NMT (b) (4) CFU/g
<i>E. coli</i> (USP <62>)	Absent in 1 g

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.

ADEQUATE

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

END

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/s/

BRYAN S RILEY
06/06/2014

JOHN W METCALFE
06/07/2014
I concur.

OPS-MICROBIOLOGY REVIEW OF PRE-NDA MEETING PACKAGE

I. NDA: 206143

REVIEW DATE: 18 November 2013

MICROBIOLOGIST: Bryan S. Riley, Ph.D.

DRUG NAME: Ivabradine Tablets

SPONSOR: Amgen

DOCUMENT DATE: 5 November 2013

CONSULT DATE: 14 November 2013

DATE ASSIGNED: 15 November 2013

DOSAGE FORM: Oral Tablet

II. MANUFACTURER:

(b) (4)

III. REVIEW NOTES:

1. BACKGROUND

This Type B meeting was requested to review the CMC data and the proposal for an NDA submission. The drug product is a film-coated tablet manufactured using (b) (4) process. The applicant has proposed microbial limit release specifications but is requesting (b) (4) for microbial limits. There was one question that was relevant to product quality microbiology.

2. DISCUSSION

Question 2: Does the Agency agree that the proposed drug substance and drug product specification strategies are appropriate for ivabradine commercial registration?

FDA Response: (b) (4)

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. (b) (4) more information on your process will be needed. Address the following points in your NDA submission:

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

- a. *Define the maximum processing time for (b) (4) step.*
- b. *Define the maximum holding time for the (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.

4. Provide the results of microbial limits testing performed on exhibit or stability batches of the drug product.

(b) (4) then remove the microbial limits tests and acceptance criteria from the drug product release specification. You should minimally perform microbial limits testing at the initial stability testing time point. Alternatively, you may retain a microbial limits specification for product release, but testing must be performed on every lot of drug product produced.

3. ADDITIONAL COMMENTS: N/A

Bryan S. Riley, Ph.D.
Team Leader (Acting)

Stephen E. Langille, Ph.D.
Master Review Microbiologist

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/s/

BRYAN S RILEY
11/18/2013

STEPHEN E LANGILLE
11/18/2013