

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206302Orig1s000

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: 28 May 2014

TO: NDA 206302

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

THROUGH: John Metcalfe, Ph.D.
Microbiologist
CDER/OPS/NDMS

cc: Michael Monteleone
Senior Regulatory Health Project Manager
CDER/OND/ODEI/DCRP

SUBJECT: Product Quality Microbiology assessment of Microbial Limits for
Nebivolol and Valsartan [Submission Date: 23 February 2014]

The Microbial Limits specification for Nebivolol and Valsartan is acceptable from a product quality microbiology perspective and is recommended for approval from the standpoint of product quality microbiology.

Nebivolol and Valsartan is a tablet for oral administration. Proposed presentations include 5 mg/80 mg (Nebivolol/Valsartan), 5 mg/160 mg, 10 mg/160 mg, 10 mg/320 mg, and 20 mg/320 mg tablets.

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). Recommended acceptance criteria in USP <1111> for product of this type include a total aerobic microbial count of 10^3 CFU/g, a total yeast and mold count of 10^2 CFU/g, and the absence of *Escherichia coli* per gram.

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

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. Microbiological testing is performed at product release and as a part of the stability program.

END

Information Request Included with 74-day Letter (06 May 2014)

You propose waiving microbial limits release testing for your drug product. This proposal may be acceptable provided adequate upstream controls are established and documented. 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. *Define the maximum processing time [REDACTED] (b) (4).*
 - b. *Define the maximum holding time for the coating solution.*
2. *Describe microbiological monitoring and acceptance criteria for the critical control points that you have identified. 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. *Verify the suitability of your microbiological testing methods for your drug product.*

15 May 2014 Response

The applicant clarified that the drug product is tested for microbial limits at product release and on stability, and that the microbiological methods are suitable for use with the drug product. The response was adequate to complete the review.

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/s/

ERIKA A PFEILER
05/28/2014

JOHN W METCALFE
05/28/2014
I concur.

PRODUCT QUALITY MICROBIOLOGY NON-STERILE

DRUG PRODUCT FILING CHECKLIST

NDA Number: 206302 **Applicant:** Forest Laboratories, Inc. **Letter Date:** 23 February 2014
Drug Name: Nebivolol and Valsartan Tablet **NDA Type:** 505(b)(2) **Stamp Date:** 24 February 2014
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		See Additional Comments.
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		

The subject drug product is a film-coated tablet for oral administration. Presentations with 5 different nebivolol/valsartan contents are described, 5/80 mg, 5/160 mg, 10/160 mg, 10/320 mg, and 20/320 mg. The drug product is produced (b)(4) [redacted]. The applicant states that microbial limits testing will be performed as a part of the stability program, but no method verification information was included. Data from stability batches of the drug product are included in the application, all product that was tested met acceptance criteria.

The following comments will be conveyed to the applicant in the 74-day letter:

You propose waiving microbial limits release testing for your drug product. This proposal may be acceptable provided adequate upstream controls are established and documented. 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. Define the maximum processing time (b) (4)
 - b. Define the maximum holding time for the coating solution.
2. Describe microbiological monitoring and acceptance criteria for the critical control points that you have identified. 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. Verify the suitability of your microbiological testing methods for your drug product.

Erika Pfeiler, Ph.D.
Microbiologist

Date

John Metcalfe, Ph.D.
Senior Review Microbiologist

Date

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
03/13/2014

JOHN W METCALFE
03/13/2014
I concur.