CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205832Orig1s000

MICROBIOLOGY / VIROLOGY REVIEW(S)

M E M O R A N D U M

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

DATE: 22 August 2014

TO: NDA 205832

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: Jessica Lee
Regulatory Health Project Manager
CDER/OND/ODEII/DPARP

SUBJECT: Product Quality Microbiology assessment of Microbial Limits for Nintedanib [Submission Date: 02 May 2014]

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

Nintedanib is a capsule 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>(Validation Report VAL 12 TS ML 098).

The Microbial Limits acceptance criteria are listed in table 1 (which is copied from the release specification in module 3.2.P.5.1 of the subject submission).

M E M O R A N D U M

Table 1. Microbial Limits Acceptance Criteria

Microbiological quality	-
	Standard test Ph.Eur./USP/JP
	(b) (4)
Test frequency: Testing performed on every batch	

ADEQUATE

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

END

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/s/

JOHN W METCALFE
08/22/2014

BRYAN S RILEY
08/22/2014
I concur.

PRODUCT QUALITY MICROBIOLOGY NON-STERILE

DRUG PRODUCT FILING CHECKLIST

NDA Number: 205832 **Applicant:** Boehringer Ingelheim Pharmaceuticals, Inc **Letter Date:** 02 May 2014

Drug Name: Nintedanib **NDA Type:** 505 (b)(1) **Stamp Date:** 02 May 2014

Dosage Form: Capsule **Reviewer:** John W. Metcalfe, PhD

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		Modules 3.2.P.2, 3.2.P.5.1, 3.2.P.8.
2	Has the applicant submitted an overall description of the manufacturing processes and microbiological controls used in the manufacture of the drug product?	X		Module 3.2.P.3.3.
3	Has the applicant submitted microbiological specifications for the drug product and a description of the test methods?	X		The product specification states that micro testing is not performed routinely.
4	Has the applicant submitted the results of analytical method verification studies?		X	
5	Has the applicant submitted preservative effectiveness studies (if applicable)?			Not applicable
6	Is this NDA fileable? If not, then describe why.	X		

Additional Comments: A Microbiology Information Request for the applicant is provided on page 2 of this review.

30 May 2014

John W. Metcalfe, Ph.D. Date
Senior Microbiology Reviewer, CDER/OPS/NDMS

30 May 2014

Bryan S. Riley, Ph.D. Date
Team Leader (Acting), CDER/OPS/NDMS

Microbiology Information Request

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. Define the maximum processing time (b) (4).

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. Describe activities taken when microbiological acceptance criteria are not met at control points.

4. You should minimally perform microbial limits testing at the initial stability testing time point. Provide an updated stability schedule to reflect this testing.

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. If you choose to test every batch, provide data from studies demonstrating suitability of use of the Microbial Limits tests with the drug product. Please submit a revised drug product release specification for whichever microbial limits testing alternative that you select.

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/s/

JOHN W METCALFE
05/30/2014

BRYAN S RILEY
05/30/2014
I concur.