

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205755Orig1s000

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: 03 March 2014

TO: NDA 205-755

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: Karen Boyd
Project manager OHOP

SUBJECT: Product Quality Microbiology assessment of Microbial Limits for Ceritinib/LDK 378 [Submission Date: 24 December 2013]

The application for Ceritinib/LDK 378 is acceptable from a Product Quality Microbiology perspective and this submission is recommended for approval.

Ceritinib/LDK 378 is a hard gelatin capsule for oral administration. The applicant originally proposed (b) (4) for microbial enumeration studies.

22 January 2014 information request

You propose (b) (4) testing for the Microbial Limits test for drug product release. (b) (4) for drug products (b) (4) 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 (b) (4). However, microbial limits testing may be omitted from the product release specification provided adequate (b) (4) 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.
2. Describe microbiological monitoring and acceptance criteria for the critical control points that you have identified. Verify the suitability of your testing methods

MEMORANDUM

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.

In addition to these points, address the following:

1. You should minimally perform microbial limits testing at the initial stability testing time point. Provide an updated stability schedule to reflect this testing.
2. In the absence of historical data, you should perform quarterly microbial limits testing on stability batches for the first year of stability. Following the first year, testing may be performed annually.

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 (b) (4) drug product produced.

Please submit a revised drug product release specification for whichever microbial limits testing alternative that you select.

Summary of response dated 19 February 2014 (eCTD sequence 0018)

The applicant indicated that they planned to waive all microbial limits testing. To support the lack of end product microbial testing, the applicant described the quality control plan. The drug substance and excipients are (b) (4) and all incoming lots are tested with USP<61> and <62> for conformance to USP<1111> or the product monograph. These tests were stated to undergo method suitability prior to execution. The entire manufacturing process (b) (4)

(b) (4) To date, all product tested for microbial enumeration (Table 1) had undetectable bioburden.

MEMORANDUM

Table 1- Results from microbial evaluation of LDK378 batches (Sponsor Table 1 from 19 February 2014)

Batch number	Storage conditions	Total aerobic microbial count [cfu/g]	Combined yeasts and molds [cfu/g]	Specified micro-organisms [<i>Escherichia coli</i>]
Requirements			(b) (4)	Not detectable in 1 g
Batches tested at release				
1010001372	Initial analysis			Absent
1010001924	Initial analysis			Absent
1010002072	Initial analysis			Absent
X275FK	Initial analysis			Absent
X324HK	Initial analysis			Absent
X325HK	Initial analysis			Absent
X398IK	Initial analysis			Absent
X399IK	Initial analysis			Absent
X400IK	Initial analysis			Absent
Batches tested after 6 months				
1010000660	25 °C/ 60% RH 6 months			Absent
101000958	25 °C/ 60% RH 6 months			Absent
Batch tested at both release and after 6 months				
1010001326	Initial analysis			Absent
	25 °C/ 60% RH 6 months			Absent

The applicant proposes to conduct USP<61> and <62> testing at 0, 12, and 24 months for the registration batches and first three commercial batches. If an extension of the expiry to (b) (4) months is deemed appropriate, then microbial evaluation will also occur at (b) (4) months.

24 February 2014 information request

Please submit a revised specification that reflects the removal of (b) (4) for microbial enumeration studies.

Summary of response dated 03 March 2014

The applicant submitted an updated testing monograph that removed reference to microbial studies conducted for release and stability. Microbial stability studies will be conducted as described above for the registration and the first three commercial scale batches only.

ADEQUATE

Reviewer Comments – The lack of (b) (4) microbiological testing for the drug product has been adequately justified. The applicant has provided data from 12 batches that demonstrate adequate microbial at release and/or 6 months. Microbial testing will be conducted for the three registration and first three commercial batches through expiry. The (b) (4) will prevent any microbial proliferation during storage. These studies are adequate to support the continued microbial control of this drug product and are consistent with Agency expectations.

END

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/s/

JESSICA COLE
03/05/2014

BRYAN S RILEY
03/06/2014
I concur.

PRODUCT QUALITY MICROBIOLOGY NON-STERILE DRUG PRODUCT FILING CHECKLIST

NDA Number: 205-755 **Applicant:** Novartis Pharmaceuticals Corporation **Letter Date:** 24 December 2013

Drug Name: ceritinib (non-proprietary) **NDA Type:** NME 505(b)(1) **Stamp Date:** 24 December 2013

Dosage Form: Oral capsule **Reviewer:** Jessica Cole, 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		
2	Has the applicant submitted an overall description of the manufacturing processes and microbiological controls used in the manufacture of the drug product?	X		(b) (4) process
3	Has the applicant submitted microbiological specifications for the drug product and a description of the test methods?	X		(b) (4) is proposed
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: This NDA has Orphan designation and will be granted a priority review.

Product Quality Microbiology Information Request:

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

In addition to these points, address the following:

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Please submit a revised drug product release specification for whichever microbial limits testing alternative that you select.

Jessica Cole, PhD	14 January 2014
_____ Reviewing Microbiologist	_____ Date
Bryan Riley, PhD	
_____ Microbiology Team Leader	_____ Date

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/s/

JESSICA COLE
01/14/2014

BRYAN S RILEY
01/14/2014
I concur.