

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**207103Orig1s000**

**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:** 04 December 2014

**TO:** NDA 207-103

**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:** Amy Tilley  
Regulatory Project Manager  
CDER/OND/OHOP/DOP1

**SUBJECT:** Product Quality Microbiology assessment of Microbial Limits for  
Palbociclib (PD-0332991) [Submission Date: 30 June 2013]

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**The application for Palbociclib is acceptable from a product quality microbiology perspective and this submission is recommended for approval.**

“Palbociclib (PD-0332991) is a capsule for oral administration. The manufacturing process is a (b) (4)

Information request dated 11 September 2014

We refer to footnote 2 in the product specification that indicates microbial limits will comply when tested. Define the proposed testing schedule for microbiological enumeration of the final drug product.

Please note that 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 (b) (4) 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.

## MEMORANDUM

a. Identify and justify critical control points in the manufacturing process that could affect microbial load of the drug product. For example, a microbial specification for incoming components would provide data to support reduced testing for this (b) (4) manufacturing process.

b. 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.

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

### Summary of response dated 23 October 2014

The applicant proposes to remove microbial enumeration from the release specification. This proposal was justified with demonstration of the control of the incoming components, the product's attributes, and the product history that demonstrates that the product consistently met the acceptance criteria. Incoming components are tested for compliance with established microbial limits for raw materials. Any lots that do not meet compendial requirements are discarded. The applicant states that the final capsules demonstrate (b) (4) levels below (b) (4), which is below the level required to support microbial growth. To date, 26 batches manufactured at Pfizer Freiburg have been tested for microbiological purity and all results were below the limit of detection for microbial quality ((b) (4) CFU/g TAMC and TYMC, with no detection of *Escherichia coli*).

### Information request dated 11 September 2014

Justify the lack of USP<62> testing on stability.

### Summary of response dated 23 October 2014

The applicant proposes to remove the specified organisms testing from the stability program. The provided justification is that the type of organisms present will not change during storage and the applicant states that the organisms were determined absent at the release for each stability batch. However, Module 3.2.P.8.2 states that only TAMC and TYMC will be conducted on stability. Thus, there will be no data to demonstrate that the drug product does not contain *Escherichia coli*.

### Information request dated 19 November 2014

We refer to your 23 October 2014 response to microbiology question 2 from the 11 September 2014 information request. In that response, the absence of USP<62> testing on stability is justified due to the conduct of USP<62> testing for *Escherichia coli* at release. However, the 23 October 2014 response to Question 1 removes release testing for microbiological enumeration from the specification. Module 3.2.P.8.2 states that microbiological testing on stability will only include total aerobic microbial count and total yeast and mold count. USP<62> testing for the absence of *E. coli* should be included on stability.

## MEMORANDUM

### Summary of response dated 26 November 2014

The applicant clarified that they intend to remove microbial enumeration from release and stability testing. The 23 October 2014 amendment was intended to propose a full waiver of microbial testing for this drug product. As the applicant has demonstrated control of the incoming components, the product's attributes, and an acceptable product history the request to remove testing is reasonable. The first three commercial batches will include microbial testing at the initial time point with TAMC and TYMC only at 12, 24, and 36 months. As the data provided are adequate to support a full waiver of microbial testing the lack of USP<62> testing at later time points for the first three commercial batches is acceptable.

### ADEQUATE

**Reviewer Comments – The microbiological quality of the drug product is assured via (b) (4) manufacturing controls. This manufacturing process is (b) (4) and 26 batches were demonstrated to meet the compendial limits for solid oral dosage forms. It is acceptable to remove the microbial enumeration for this low risk solid oral dosage form.**

END

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/s/  
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JESSICA COLE  
12/08/2014

BRYAN S RILEY  
12/08/2014  
I concur.

# PRODUCT QUALITY MICROBIOLOGY NON-STERILE DRUG PRODUCT FILING CHECKLIST

**NDA Number:** 207-103      **Applicant:** Pfizer, Inc.      **Letter Date:** 30 June 2014  
**Drug Name:** Palbociclib (PD-0332991)      **NDA Type:** 505(b)(1)      **Stamp Date:** 30 June 2014  
**Dosage Form:** Capsule      **Reviewer:** Jessica G. 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)
3	Has the applicant submitted microbiological specifications for the drug product and a description of the test methods?	X		Intermittent (undefined) testing is proposed
4	Has the applicant submitted the results of analytical method verification studies?	X		
5	Is this NDA fileable? If not, then describe why.	X		

Additional Comments: This priority NDA is indicated for the treatment of advanced breast cancer.

Product Quality Microbiology Information Request:

1. We refer to footnote 2 in the product specification that indicates microbial limits will comply when tested. Define the proposed testing schedule for microbiological enumeration of the final drug product.

Please note that 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 (b) (4) 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.

a. Identify and justify critical control points in the manufacturing process that could affect microbial load of the drug product. For example, a microbial specification for incoming components would provide data to support reduced testing for this (b) (4) manufacturing process.

b. 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.

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

2. Justify the lack of USP<62> testing on stability.

Jessica G. Cole, PhD

03 September 2014

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Reviewing Microbiologist

Date

Bryan Riley, PhD

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Microbiology Team Leader

Date

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/s/  
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JESSICA COLE  
09/11/2014

BRYAN S RILEY  
09/11/2014  
I concur.