

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205410Orig1s000

MICROBIOLOGY REVIEW(S)

MEMORANDUM



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

DATE: 05 December 2013

TO: NDA 205410

FROM: Erika Pfeiler, Ph.D.
Microbiologist

THROUGH: John Metcalfe, Ph.D.
Senior Review Microbiologist

cc: Quynh Nguyen
CDER/OND/ODEI/DCRP

SUBJECT: Product Quality Microbiology assessment of Microbial Limits for Propranolol Oral Solution [Submission Date: 17 May 2013]

The microbial limits specifications for Propranolol are acceptable from a Product Quality Microbiology perspective. Therefore, this submission is recommended for approval from the standpoint of product quality microbiology.

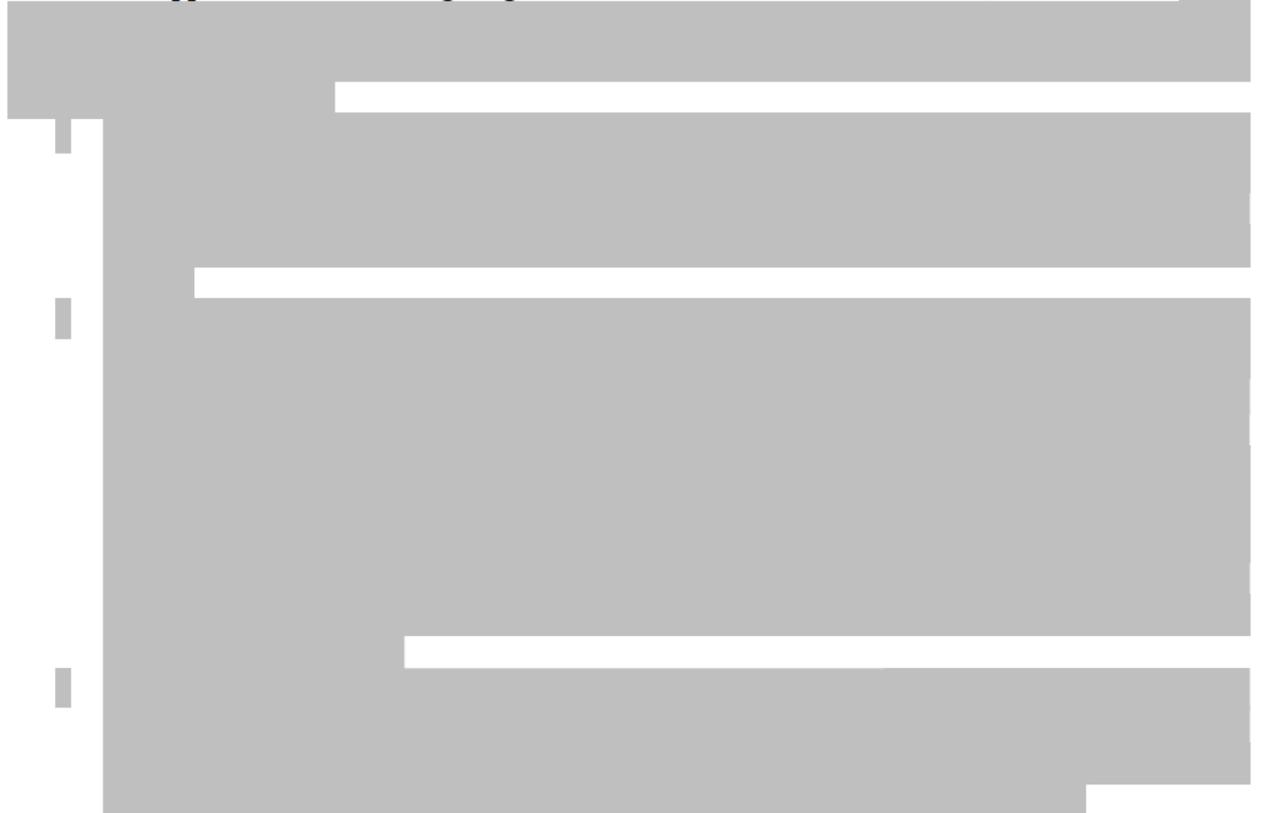
Propranolol is an aqueous solution for oral administration in the treatment of proliferating infantile hemangiomas.

As a part of pharmaceutical development, antimicrobial effectiveness testing and microbiological in-use testing were performed. The drug product [REDACTED] ^{(b) (4)} was demonstrated to be self-preserving in antimicrobial effectiveness testing which used methods described in USP <51> and met the requirements for category 3 products. In-use testing was performed, which demonstrated that after 60 days of sampling, the product maintained the microbial limits at release. However, it is unclear in this testing whether product was administered to a patient, which would represent a worst-case for microbial contamination.

The drug product is tested for microbial limits at release using a method consistent with USP Chapter <61> and <62>. The Microbial Limits acceptance criteria are consistent with USP Chapter <1111> which include a total aerobic microbial count of 10^2 , a total yeast and mold count of 10^1 and the absence of *Escherichia coli*. 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 applicant presented a risk assessment that identified possible ways in which the final drug product could become contaminated with *Burkholderia cepacia*. The risk assessment identified the most critical areas of risk to be the (b) (4) water used in production, the drug product composition (aqueous, (b) (4) nonsterile), and lack of methods to test the drug product or (b) (4) water. The applicant outlined mitigating actions based on this risk assessment, which include (b) (4)



Based on the results of these tests, and with ongoing monitoring activities in place, the applicant states that adequate controls are in place to prevent contamination of the drug product by *B. cepacia*.

The drug product will be tested for microbial limits annually as part of the post-approval stability protocol at 0, 12, 24, and 36 months, along with antimicrobial effectiveness testing. Testing for specified microorganisms will not be performed as part of the stability program.

ADEQUATE

Reviewer Comments – The microbiological quality of the drug product is controlled via suitable manufacturing controls and testing protocols.

Filing Review Information Request

Non-sterile aqueous drug products may potentially be contaminated with organisms in the Burkholderia cepacia complex (BCC). BCC strains have a well-documented ability to ferment a wide variety of substrates and are known to proliferate in the presence of many traditional preservative systems. Thus, despite the presence of otherwise adequate preservative systems, BCC strains can survive and even proliferate in product during storage. For a recent review of FDA's perspective on BCC please see PDA J Pharm Sci Tech 2011; 65(5): 535-43. In order to control for the presence of BCC in your product you should consider the following:

MEMORANDUM

Identify potential sources for introduction of BCC during the manufacturing process and describe the steps to minimize the risk of BCC organisms in the final drug product. We recommend that potential sources are examined and sampled as process controls. These may include raw materials and the manufacturing environment. A risk assessment for this species in the product and raw materials is recommended to develop sampling procedures and acceptance criteria.

Provide test methods and acceptance criteria to demonstrate the drug product is free of BCC. Your test method should be validated and a discussion of those methods should be provided. Test method validation should address multiple strains of the species and cells should be acclimated to the conditions in the manufacturing environment (e.g., temperature) before testing.

As there are currently no compendial methods for detection of BCC, we have provided suggestions for a potential validation approach and some points to consider when designing your validation studies. However, any validated method capable of detecting BCC organisms would be adequate. It is currently sufficient to precondition representative strain(s) of BCC in water and/or your drug product (b) (4) to demonstrate that your proposed method is capable of detecting small numbers of BCC. Your submission should describe the preconditioning step (time, temperature, and solution(s) used), the total number of inoculated organisms, and the detailed test method to include growth medium and incubation conditions. It is essential that sufficient preconditioning of the organisms occurs during these method validation studies to insure that the proposed recovery methods are adequate to recover organisms potentially present in the environment.

*For more information, we refer you to *Envir Microbiol* 2011; 13(1):1-12 and *J. Appl Microbiol* 1997; 83(3):322-6.*

14 November 2013 Response

The applicant provided information to complete the review. Additional questions were submitted to the applicant in a subsequent information request.

19 November 2013 Information Request

*We acknowledge your 17 May 2013 NDA submission and your 14 November 2013 information request response that addressed *Burkholderia cepacia* control and testing. More information is needed. Your 14 November 2013 information request response states that the (b) (4) (b) (4) is monitored for microbiological quality. Please address the following points.*

- a. You state that the microbiological monitoring test method is "validated on BCC." Provide a description of this test method, as well as validation data that support its use in detecting organisms of the *Burkholderia cepacia* complex.*
- b. What is the frequency with which you monitor the (b) (4) (b) (4) for microbial limits and the absence of specified microorganisms?*

03 December 2013 Response

The applicant provided information that was adequate to complete the review.

END

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/s/

ERIKA A PFEILER
12/05/2013

JOHN W METCALFE
12/05/2013
I concur.

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Erika Pfeiler, Ph.D.
Microbiologist

Date

John Metcalfe, Ph.D.
Senior Review Microbiologist

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/s/

ERIKA A PFEILER
06/03/2013

JOHN W METCALFE
06/03/2013
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