

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205474Orig1s000**

**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:** 23 July 2014

**TO:** NDA 205474

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

**THROUGH:** Stephen Langille, Ph.D.  
Senior Review Microbiologist  
CDER/OPS/NDMS

**cc:** Laura Musse  
Regulatory Health Project Manager  
CDER/OND/ODEII/DPARP

**SUBJECT:** Product Quality Microbiology assessment of Microbial Limits for Hydrocodone Bitartrate and Guaifenesin [Submission Date: 14 January 2014]

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**The microbial limits specification for Hydrocodone Bitartrate and Guaifenesin is acceptable from a Product Quality Microbiology perspective. Therefore, this submission is recommended for approval from the standpoint of product quality microbiology.**

The drug product is a nonsterile oral solution, 2.5 mg/5 mL with raspberry and cherry punch flavors.

The drug product contains methylparaben (b) (4) and propylparaben (b) (4) (b) (4). As part of product development, testing was performed on product (b) (4)

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

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Preparations and Substances for Pharmaceutical Use). Limits listed in Chapter <1111> for products of this type state NMT (b)(4) total aerobic microbial count, NMT (b)(4) total yeast and mold count, and the absence of *Escherichia coli* and *Burkholderia cepacia* per mL. The microbial enumeration and test for the absence of *E. coli* methods were verified to be appropriate for use with the drug product following procedures consistent with those in USP Chapter <61> and <62>. The applicant performed validation studies demonstrating the adequacy of their test method for detection of *B. cepacia*. In addition to testing for *B. cepacia* at product release, the applicant states that the (b)(4) water system at the manufacturing site is monitored for *B. cepacia*.

The drug product will also be tested for microbial enumeration, the absence of *E. coli* and antimicrobial effectiveness 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.**

*05 June 2014 Information Request*

*Your application contains study reports from USP <51> Antimicrobial Effectiveness Testing, but you do not provide reports from your pharmaceutical development studies in which you tested drug product (b)(4). Provide these reports.*

*22 July 2014 Response*

*The applicant provided the requested information.*

*05 June 2014 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 (b)(4) 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:*

- 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 without preservatives to demonstrate that your proposed method is capable of detecting small numbers of BCC. Your submission should*

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*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.*

*01 July 2014 Response*

*The applicant commits to including a specification for the absence of B. cepacia in the finished drug product. In addition, the applicant states that B. cepacia monitoring is performed in the (b) (4) water system at the manufacturing site.*

**END**

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ERIKA A PFEILER  
07/23/2014

STEPHEN E LANGILLE  
07/23/2014