

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
022424Orig1s000

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 December 2014

TO: File: NDA 22-424

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

SUBJECT: NDA 22-424 Resubmission (Response to Microbiology Deficiency)
Submission Date: 18 November 2014
Drug Product: Hydrocodone and Guaifenesin Oral Solution
Sponsor: Mikart, Inc.

Recommendation – The applicant has adequately addressed the microbiology deficiency from the 28 September 2011 Complete Response Letter. Therefore, this submission is recommended for approval from the standpoint of product quality microbiology.

Background

The drug product is a solution for oral administration. A Complete Response Letter was issued to the subject NDA on 28 September 2011. The Complete Response Letter contained one microbiology deficiency, which is copied below.

Your proposed drug product release specification lacks a test and acceptance criterion for Burkholderia cepacia, an organism considered objectionable in non-sterile aqueous drug products.

This deficiency may be addressed by doing the following:

- a. Incorporate testing and acceptance criteria for the bacteria, Burkholderia cepacia, into the release specification for your proposed hydrocodone and guaifenesin combination product.*
- b. Provide test method(s) for Burkholderia cepacia and the relevant method validations. The test method(s) validation should address multiple strains of the*

MEMORANDUM

species and cells that are acclimated to the environments (e.g., warm or cold water) that may be tested.

The subject submission includes a response to this deficiency. The drug product release and stability (timepoints: 18, 24 and 36 months) specifications have each been updated to include testing for *Burkholderia cepacia*. The acceptance criterion for this test is “absent”. The test for *Burkholderia cepacia* was developed by the applicant since there is currently no compendial test method, and is described in module 3.2.P.5.2. The method involves (b) (4)

The test method validation is summarized in a report entitled, *Validation of the Method Suitability Testing for the Absence of Burkholderia cepacia for HB and Guaifenesin and HB & Guaifenesin & Pseudoephedrine HCl Oral Solution* (provided in module 3.2.R.3.P.9 of the subject amendment). Briefly, the validation was performed (b) (4)

after which the test method was performed as described above. The positive controls used the same challenge bacteria inoculated (b) (4) (without drug product), and the negative controls were (b) (4) samples without product or challenge bacteria. Both *Pseudomonas aeruginosa* and *Staphylococcus aureus* were included in the validation to demonstrate the selective medium’s ability to inhibit these organisms. The acceptance criteria for this study included the following:

- *The specified microorganisms must be detected from the test material sample, as well as, from the positive control sample. The negative control plates show no microbial growth*

The validation report states that *Burkholderia cepacia* were recovered from BCSA in two separate studies performed by two different analysts (page 7 of the validation report). The challenge organisms were identified successfully using the Biolog Identification system.

Satisfactory

Reviewer’s Comment

The applicant has adequately addressed the microbiology deficiency from the 28 September 2011 Complete Response Letter.

END

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/s/

JOHN W METCALFE
12/08/2014

BRYAN S RILEY
12/08/2014
I concur.

Product Quality Microbiology Review

16 August 2011

NDA: 22-424/N-000

Drug Product Name

Proprietary:

N/A.

Non-proprietary:

Hydrocodone Bitartrate
Guaifenesin.

Review Number: 1.

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
29 NOV 2010	29 NOV 2010	N/A	N/A
16 MAY 2011	17 MAY 2011	26 JUL 2011	04 AUG 2011

Applicant/Sponsor

Name:

Tiber Laboratories, LLC.

Address:

5400 Laurel Springs Parkway,
Suite 803.
Suwanee, GA 30024.

Representative:

Cassie Vitolo

Telephone:

678-208-0388

Name of Reviewer:

John W. Metcalfe, Ph.D.

Conclusion:

Approvable, pending resolution
of microbiology deficiencies.

Product Quality Microbiology Data Sheet

- A.
1. **TYPE OF SUBMISSIONS:** 505(b)(2) NDA and Amendment.
 2. **SUBMISSION PROVIDES FOR:** Marketing Authorization (original NDA) and responses to Chemistry Information Request (amendment).
 3. **MANUFACTURING SITE:**
Mikart, Inc.
2090 Marietta Blvd.
Atlanta, GA 30318
 4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**
 - Non-sterile solution.
 - Oral.
 - 2.5 mg/5 mL hydrocodone bitartrate, and 200 mg/5 mL guaifenesin.
 5. **METHOD(S) OF STERILIZATION:** The product is non-sterile.
 6. **PHARMACOLOGICAL CATEGORY:** The drug product is indicated for the treatment of cough.
- B. **SUPPORTING/RELATED DOCUMENTS:** None.
- C. **REMARKS:**
The subject NDA is submitted electronically in the CTD format.

A Chemistry Information Request was forwarded to the applicant in a Filing Communication on 11 February 2011. The requested information included questions pertaining to microbiology issues. The applicant provided responses to this Information Request in an amendment dated 16 May 2011. The New Drug Microbiology Staff was consulted by ONDQA for review of these responses on 26 July 2011, and this reviewer received the assignment on 04 August 2011.

Following is the microbiology question that was provided to the applicant:

- *Provide written methods for the microbial limits test procedure [REDACTED] (b) (4) [REDACTED] for the drug product, along with appropriate validation data.*

This reviewer's assessment of the applicant's responses to these microbiology questions is provided in appropriate sections of this review.

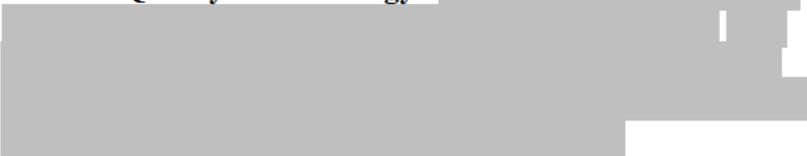
File Name: N022424R1.doc

Executive Summary

I. Recommendations

- A. Recommendation on Approvability** – NDA 22-424/N-000 is approvable pending resolution of the microbiology deficiencies.
- B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable** – Not applicable.

II. Summary of Microbiology Assessments

- A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology** -  (b) (4)

- B. Brief Description of Microbiology Deficiencies** – The drug product release specification lacks a test and acceptance criterion for *Burkholderia cepacia*, an organism considered objectionable in non-sterile aqueous drug products.
- C. Assessment of Risk Due to Microbiology Deficiencies** – There is a small risk of microbial contamination of the subject drug product due to the microbiology deficiencies identified on Page 9 of this review.

III. Administrative

- A. Reviewer's Signature** _____
John W. Metcalfe, Ph.D.
- B. Endorsement Block** _____
Stephen Langille, Ph.D.
- C. CC Block**
N/A

Product Quality Microbiology Assessment

**1. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q)
MODULE 3.2: BODY OF DATA**

S DRUG SUBSTANCE

The drug substance manufacturing process is not the focus of this review.

P DRUG PRODUCT

P.1 Description of the Composition of the Drug Product

• **Description of drug product**

The subject drug product is a (b) (4) solution presented as either a 4 ounce or 16 ounce packaging size.

• **Drug product composition**

The drug product composition is presented in Table 1 which is copied from Table 3.2.P.1.2 of the subject submission.

Table 1. Drug Product Composition.

Component	Mikart Code#	Reference	Pharmaceutical Function	Formula (%)
Active Ingredients				
Hydrocodone Bitartrate USP	0127	USP	Active	0.05%*
Guaifenesin USP	1030	USP	Active	4.00%**
Inactive Ingredients				
Sorbitol (b) (4) USP	(b) (4)	USP		(b) (4)
Glycerin USP		USP		
Saccharin Sodium USP		USP		
Polyethylene Glycol (b) (4) NF		NF		
(b) (4) Black Raspberry Flavor	(b) (4)	N/A		
FD&C Blue #1	(b) (4)	N/A		
D&C Red #33		N/A		
Methylparaben NF		NF		
Propylparaben NF		NF		
Citric Acid (b) (4) USP		USP		
Sodium Citrate USP		USP		
Purified Water USP		USP		

* Equivalent to 2.5 mg hydrocodone bitartrate per 5 mL

** Equivalent to 200 mg guaifenesin per 5 mL

• **Description of container closure system**

The drug product container closure systems are presented in Table 2 which is copied from Module 3.2.P.1.3 of the subject submission.

Table 2. Container Closure Systems.

4 oz Packaging Size Lot # B100058B

(b) (4)



16 oz Packaging Size Lot # B100056A, B100057A, B100058A

(b) (4)



P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

(b) (4)



Satisfactory

P.3 Manufacture

P.3.1 Manufacturer

Mikart, Inc.
 2090 Marietta Blvd.
 Atlanta, GA 30318

P.3.3 Description of the Manufacturing Process and Process Controls

(b) (4)

(Module 3.2.R).

P.5 Control of Drug Product

P.5.1 Specification

The product release specification includes the test methods and acceptance criteria shown in Table 3 which are indicators of the microbiological quality of the subject drug product.

Table 3. Microbiological Release Tests and Acceptance Criteria.

Test	Method	Acceptance Criteria
(b) (4)		
<u>Microbial Limits</u>		
• Total Plate Count	NMT (b) (4)	USP<61>
• Total combined molds and yeasts count	NMT (b) (4)	USP<61>
• <i>Escherichia coli</i>	Absent	USP<62>

P.5.2 Analytical Procedures

• **Microbial Limits**

The applicant performs microbial limit testing using the pour plate method according to USP<61> and <62>. SOP 147 was provided in the subject amendment and describes verification of the suitability of use of the microbial limits tests with the subject drug product. The challenge microbes used in this verification study are consistent with those that are suggested in USP<61> and <62>. The methods described in SOP 147 allow for a demonstration of the test suitability, as required in the USP chapters.

Data are provided in the subject amendment from verification studies demonstrating the suitability of the microbial limits tests with the

subject drug product (Lot No. M4921). The challenge microbes used in this study included the following:

- *Escherichia coli*
- *Staphylococcus aureus*
- *Pseudomonas aeruginosa*
- *Candida albicans*
- *Bacillus subtilis*
- *Aspergillus brasiliensis*

The verification test data are provided in the report and are acceptable.

Not Satisfactory

Reviewer Comments

1. The microbial limits test methods and associated verification studies for total aerobic plate count and total yeasts and molds are acceptable.
2. Reference is made to the applicant's microbial limit acceptance criteria of NMT (b) (4) yeast/molds, NMT (b) (4) CFU Total Plate Count and an absence of *Escherichia coli*. The acceptance criteria do not specify an amount of drug product tested (e.g.: per gram). The applicant should:
 - Correct the acceptance criteria to identify an amount of drug product tested.
 - (b) (4) be consistent with the value suggested in USP<1111> for aqueous preparations for oral use.
3. *Burkholderia cepacia* is considered an objectionable organism with regard to non-sterile, aqueous drug products. The applicant should:
 - Provide test methods and acceptance criteria to demonstrate the product is free of the objectionable microorganism *Burkholderia cepacia*. We recommend that potential sources are examined and sampled as process controls, and 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. Your test method should be validated and a discussion of those methods should be provided. Test methods validation should address multiple strains of the species and cells that are acclimated to the environments (e.g., warm or cold water) that may be tested.
 - Modify the drug product release specification regarding Microbial Limits testing to include a test and acceptance criterion (absence) for *Burkholderia cepacia*.

P.7 Container Closure System

Reference is made to Section P.1 of this review.

P.8 Stability

P.8.1 Stability Summary and Conclusion

The stability specification includes the following microbiological tests and related acceptance criteria which is copied from Page 2 of 2 of Module 3.2.P.8.3.1 of the submission:

TEST	LABEL CLAIM	LIMITS	RESULTS	DATE/DONE BY
(b) (4)				
(b) (4)				
MICROBIAL LIMITS*				
TOTAL PLATE COUNT		NMT (b) (4)		
<i>ESCHERICHIA COLI</i>		ABSENT		
TOTAL COMBINED MOLDS AND YEASTS COUNT		NMT (b) (4)		
(b) (4)				

P.8.2 Post-Approval Stability Protocol and Stability Commitment

The applicant commits to the placement of the first three production batches and an annual batch thereafter, into the stability testing program (Module 3.2.P.8.2).

P.8.3 Stability Data

The subject submission contains stability data from Lots 100057A (16Oz), 100058A (16Oz), 100058B (4Oz), 100056A (16Oz) and 100057A (16Oz). Each of these lots was tested for the microbiological attributes listed in Section P.8.1 (above). The data meet acceptance criteria.

Satisfactory

A APPENDICES**A.2 Adventitious Agents Safety Evaluation**

Not applicable.

A.2.1 Materials of Biological Origin

Not applicable.

A.2.2 Testing at Appropriate Stages of Production

Not applicable.

A.2.3 Viral Testing of Unprocessed Bulk

Not applicable.

A.2.4 Viral Clearance Studies

Not applicable.

R REGIONAL INFORMATION**R.1 Executed Batch Record**

Executed batch records are provided in Module 3.2.R of the application.

2. REVIEW OF COMMON TECHNICAL DOCUMENT QUALITY (CTD-Q) MODULE 1**A. PACKAGE INSERT**

This reviewer has no comment regarding the package insert.

3. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS:

1. Reference is made to Table 3.2.P.5.1 which provides the drug product specification. The microbial limit acceptance criteria of NMT (b) (4) yeast/molds, NMT (b) (4) Total Plate Count and an absence of *Escherichia coli* do not specify an amount of drug product tested (e.g.: per gram).
 - Correct the acceptance criteria to identify an amount of drug product tested.
 - (b) (4) be consistent with the value suggested in USP<1111> for aqueous preparations for oral use.
2. *Burkholderia cepacia* is considered an objectionable organism with regard to non-sterile, aqueous drug products.
 - Provide test methods and acceptance criteria to demonstrate the product is free of the objectionable microorganism *Burkholderia cepacia*. We recommend that potential sources are examined and sampled as process controls, and 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. Your test method should be validated and a discussion of those methods should be provided. Test methods validation should address multiple strains of the species and cells that are acclimated to the environments (e.g., warm or cold water) that may be tested.
 - Modify the drug product release specification regarding Microbial Limits testing to include a test and acceptance criterion (absence) for *Burkholderia cepacia*.

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/s/

JOHN W METCALFE
08/16/2011

STEPHEN E LANGILLE
08/16/2011