CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22279Orig1s000

MICROBIOLOGY / VIROLOGY REVIEW(S)

M E M O R A N D U M

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

DATE: February 04, 2015

TO: Division of Pulmonary, Allergy, and Rheumatology Products

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Recommendation to accept data without on-site inspection**

RE: NDA 022279 and NDA 022424

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

OSIS inspected the site listed below within the last four years. The inspectional outcomes from the inspections were classified as No Action Indicated (NAI).

Requested Site Inspection

Facility Type	Facility Name	Facility Address
Analytical	(b) (4)	
Clinical	Novum Pharmaceutical Research Services	3760 Pecos McLeod, Las Vegas, NV, 89121

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/s/

SHILA S NKAH
02/04/2015

Product Quality Microbiology Review

January 14, 2015

NDA: 22-279/N-000

Drug Product Name
Proprietary: N/A
Non-proprietary: Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution.

Review Number: 2

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
July 18, 2011	July 19, 2011	January 3, 2012	January 3, 2012
Re-Submission	December 2, 2014	N/A	December 19, 2014

Submission History (for 2nd Reviews or higher) – N/A

Applicant/Sponsor
Name:
Address:

Representative:
Telephone:

(b) (4)

Name of Reviewer: Vinayak B. Pawar, Ph.D.

Conclusion: Recommend Approval

Product Quality Microbiology Data Sheet

A. **1.** **TYPE OF SUBMISSION:** 505(b)(2) NDA Resubmission.

2. **SUBMISSION PROVIDES FOR:** Responses to IR Letter of 1/11/2012.

3. **MANUFACTURING SITE:** Mikart, Inc., 2090 Marietta Blvd., Atlanta, GA 30318

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Oral, Non-sterile solution:
2.5 mg/ 5 mL hydrocodone bitartrate, 30 mg/5 mL pseudoephedrine hydrochloride and 200 mg/5 mL guaifenesin.

5. **METHOD(S) OF STERILIZATION:** Non-Sterile

6. **PHARMACOLOGICAL CATEGORY:** The drug product is indicated for the treatment of cough.

B. **SUPPORTING/RELATED DOCUMENTS:** None

C. **REMARKS:** This paper submission received on December 2, 2014 is a response to the deficiencies cited in the product Microbiology Review dated January 5, 2012 and the subsequent IR from the Agency dated January 11, 2012. A scanned copy of the submission was provided for review. The original was retrieved later for clarity.

filename: **N022279R2**

Executive Summary

I. Recommendations

A. Recommendation on Approvability - Recommend Approval

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – This submission contained a response to the deficiencies. (b) (4)

(b) (4)

B. Brief Description of Microbiology Deficiencies - None

C. Contains Potential Precedent Decision(s) - ☐ **Yes** ☒ **No**

III. Administrative

A. Reviewer's Signature _____
Vinayak B. Pawar, Ph.D.

B. Endorsement Block _____
Stephen E. 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 – Not the subject of this review.

P DRUG PRODUCT

A list of deficiencies were cited in the Microbiology Product Quality review of this NDA dated January 5, 2012. The sponsor responded to these deficiencies on December 2, 2014. Only the sponsor's response is reviewed here and is the subject of this review.

Deficiency 1: Microbial Limits Testing.

Reference is made to Module 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) CFU Total Plate Count and an absence of *Escherichia coli* do not specify an amount of drug product tested (e.g.: per ml). In addition, the application does not contain methods and datasets which verify the suitability of use of the microbial limits tests with the subject drug product.

- Correct the acceptance criteria to identify an amount of drug product tested.
- Lower the criterion for yeast/molds to be consistent with the value suggested in USP<1111> for aqueous preparations for oral use.
- Provide methods and datasets which verify the suitability of use of the microbial limits tests with the subject drug product.

Sponsor Response:

(b) (4) performed the Microbial Limits Testing and the report as well as data summary was provided on pages 428-449. Policy and Procedures [SOP 147 & 148] to meet USP <61> and <62> requirements were provided on pages 483-497.

Hydrocodone, Guaifenesin and Pseudoephedrine HCL Oral Solution, when run at a 1:10 dilution in pH 7. 2 phosphate buffer did not exhibit inhibitory properties against the test organisms Staphylococcus aureus, *Pseudomonas aeruginosa, Bacillus subtilis, Candida albicans, and Aspergillus brasiliensis* when employing the pour plate procedure for the total aerobic plate count, and yeast and mold count. Test product also did not exhibit inhibitory properties against the test organism *Escherichia coli* at a 1:10 dilution in pH 7.2 phosphate buffer in testing for this specified organism. Based on the test results, the product can be tested via the aerobic plate count procedure for bacteria, yeast, and mold at a 1:10 dilution *in* pH 7.2 phosphate buffer, and also for the indicator organism *Escherichia coli* at a 1:10 dilution in pH 7.2 phosphate buffer.

The revised finished drug product specifications which address bullet points 1 &

2 are provided in Table 1 (copied from Table 1, page 2, Attachment 2, signed 10/10/2014)

Table 1. Finished Drug Product Specifications

PRODUCT NAME: HYDROCODONE BITARTRATE, GUAIFENESIN, AND PSEUDOEPHEDRINE HYDROCHLORIDE ORAL SOLUTION (b) (4) (A)NDA #: 22-279 STRENGTH: 2.5 mg/200 mg/30 mg per 5 mL			
PRODUCT DESCRIPTION			
LIQUID	TABLET	COATED TABLET	CAPSULE
COLOR: (b) (4) (b) (4) Raspberry	COLOR: SHAPE: DEBOSS: SIDE A: SIDE B: WEIGHT PER UNIT:	COLOR: COATED: UNCOATED: SHAPE: DEBOSS: SIDE A: SIDE B: WEIGHT PER UNIT: (uncoated)	COLOR: BODY: CAP: IMPRINT: BODY: CAP: IMPRINT COLOR: WEIGHT PER UNIT: (net)

TEST	LABEL CLAIM	LIMITS	RESULTS	DATE/DONE BY
(b) (4)				
MICROBIAL LIMITS TOTAL PLATE COUNT *ESCHERICHIA COLI* *BURKHOLDERIA CEPACIA* TOTAL COMBINED MOLDS AND YEASTS COUNT		NMT (b) (4) CFU/mL ABSENT ABSENT NMT (b) (4) CFU/mL		
(b) (4)				
ADDITIONAL TESTING-NOT REQUIRED FOR RELEASE				
ANTIMICROBIAL (b) (4) EFFECTIVENESS TEST**		(b) (4)		
(b) (4)				

Deficiency 2: Absence of *Burkholderia cepacia*

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*.

Sponsor Response:

In response to bullet point 1, Validation of the Method Suitability Testing for the Absence of *Burkholderia cepacia* for HB & Guaifenesin and HB & Guaifenesin

& Pseudoepbedrine HCI Oral Solution was performed and approved on February 27, 2012 [Attachment 5]. The test procedure consisted of preparation of test strains, test material and a positive and negative control as outlined in Sections C, D and E respectively. This validation was performed using 3 different ATC'C strains of *B. cepacia*:17460, 25416 and 700450. The validation was designed to recover these microorganisms from two different formulations: Hydrocodone Bitartrate and Guaifenesin Oral Solution (HBG), (b) (4) and Hydrocodone Bitartrate, Guaifenesin and Pseudoephedrine Hydrochloride Oral Solution (HBOP), (b) (4) This validation protocol was performed by two analysts for the purposes of the Ruggedness, and Repeatability studies. The first analyst used *B. cepacia* Selective agar as selective medium, while the second analyst used PC agar. Note: Sponsor's response package was delayed due to other CMC deficiencies that needed to be addressed.

The following Acceptance Criteria was established:

1. 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.
2. Failure of the organism(s) to grow in the relevant medium and tests conditions described above, invalidates that portion of the examination and necessitates a modification of the procedure by:
   a. An increase in the volume of the diluent (the quantity of the test material remaining the same).
   b. Incorporation of a sufficient quantity of a specific or general neutralizing agent (s) into the diluent. Referenced in Table 1, page 427.
   c. Consideration of the optimum incubation conditions.
   d. An appropriate combination of the above modifications.

Conclusion: If in spite of the incorporation of suitable inactivating agents and Substantial increase in the volume of diluent it was still not possible to recover the viable cultures, it can be assumed that the failure to isolate the inoculated organism is attributable to the antibacterial activity of the product. The sponsor assures that the results serve to indicate that the product is not likely to be contaminated with the given species of microorganisms.

Response to bullet point 2 is provided in Table 1 above, which includes test and acceptance criteria for the absence of *Burkholderia cepacia*.

ADEQUATE

REVIEW COMMENT: The deficiencies were adequately addressed and meets the regulatory requirements for an aqueous oral dosage form

END

Digitally signed by Vinayak B Pawar -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300151299, cn=Vinayak B Pawar -A
Date: 2015.01.16 13:22:46 -05'00'

Stephen E. Langille -A

Digitally signed by Stephen E. Langille -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300151320, cn=Stephen E. Langille -A
Date: 2015.01.16 16:22:22 -05'00'

Product Quality Microbiology Review

05 January 2012

NDA:	22-279/N-000
Drug Product Name	
Proprietary:	N/A.
Non-proprietary:	Hydrocodone, Pseudoephedrine and Guaifenesin Oral Solution.
Review Number:	1.

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
18 JUL 2011	19 JUL 2011	03 JAN 2012	03 JAN 2012

Applicant/Sponsor	
Name:	(b) (4)
Address:	
Representative:	
Telephone:	
Name of Reviewer:	John W. Metcalfe, Ph.D.
Conclusion:	Approvable pending resolution of the microbiology deficiencies.

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSIONS: 505(b)(2) NDA Resubmission.

2. SUBMISSION PROVIDES FOR: Responses to CR Letter of 1/25/2011.

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, 30 mg/5 mL pseudoephedrine hydrochloride 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 in paper. A scanned copy of the CMC section was provided for review.

File Name: N022279R1.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability – NDA 22-279/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 - The drug product solution is

(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 10 of this review.

III. Administrative

A. Reviewer's Signature _____

John W. Metcalfe, Ph.D.

B. Endorsement Block_____

Stephen E. 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 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%**
Pseudoephedrine Hydrochloride USP	1031	USP	Active	0.60%***
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
*** Equivalent to 30 mg pseudoephedrine hydrochloride 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

	Container	Closure
Code#	(b) (4)	(b) (4)
Description	(b) (4) 4 oz (b) (4) (b) (4) opaque-white HDPE bottle	White (b) (4) (b) (4) cap with (b) (4) (b) (4) (b) (4)
Manufacturer	(b) (4)	

16 oz Packaging Size Lot # B100056A, B100057A, B100058A

	Container	Closure
Code#		(b) (4)
Description	(b) (4) 16 oz. (b) (4) (b) (4) opaque-white HDPE bottle	(b) (4) White (b) (4)
Manufacturer		(b) (4)

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

- **Preservative Effectiveness**

  The antimicrobial preservative effectiveness testing was summarized in Module 3.2.P.5.6. The test was performed according to USP<51> and utilized the following challenge organisms:

  - *Escherichia coli*
  - *Staphylococcus aureus*
  - *Pseudomonas aeruginosa*
  - *Candida albicans*
  - *Aspergillus niger*

  Data from antimicrobial effectiveness testing are presented in Module 3.2.P.5.6 and meet the USP<51> acceptance criteria for oral dosage forms.

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)

(b) (4)

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)		
Microbial Limits	USP<61>	
• Total Plate Count		NMT (b) (4) CFU
• Total combined molds and yeasts count		NMT (b) (4) CFU
• *Escherichia coli*		Absent

*This information is taken from Module 3.2.P.5.1.

P.5.2 Analytical Procedures

- **Microbial Limits**

The applicant performs microbial limit testing using the pour plate method according to USP<61>. The application does not provide verification studies of the suitability of use of the microbial limits tests with the subject drug product.

Not Satisfactory

Reviewer Comments

1. The applicant should provide test methods and datasets demonstrating the suitability of use of the microbial limits tests with the subject drug product.
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.
    - Lower the criterion for yeast/molds to 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 Module 3.2.P.8.2 of the submission:

[redacted] (b) (4)			Same as Release Specification
			Same as Release Specification
Microbiological Testing	<61>		
- Total Plate Count (TPC)		NMT (b) (4) CFUs	Same as Release Specification
- Total Combined Yeasts and Molds Count		NMT CFUs	Same as Release Specification
- E. Coli Test		Negative	Same as Release Specification

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 L4917A, L4917, M4922. 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 Module 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) CFU Total Plate Count and an absence of *Escherichia coli* do not specify an amount of drug product tested (e.g.: per gram). In addition, the application does not contain methods and datasets which verify the suitability of use of the microbial limits tests with the subject drug product.
   - Correct the acceptance criteria to identify an amount of drug product tested.
   - Lower the criterion for yeast/molds to be consistent with the value suggested in USP<1111> for aqueous preparations for oral use.
   - Provide methods and datasets which verify the suitability of use of the microbial limits tests with the subject drug product.

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*.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOHN W METCALFE
01/05/2012

STEPHEN E LANGILLE
01/05/2012