

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**022424Orig1s000**

**CHEMISTRY REVIEW(S)**

# **Chemistry Review Cover Sheet**

**NDA 22424**

**FLOWTUSS**

**Hydrocodone Bitartrate and  
Guaifenesin Oral Solution**

**Arthur B. Shaw, Ph.D.**

**OPQ/ONDP/DNDPII/NDPBIV**

**Reviewed for DPARP**

# Chemistry Review Data Sheet

1. NDA 22424
2. REVIEW #2
3. REVIEW DATE: April 24, 2015
4. REVIEWER: Arthur B. Shaw, Ph.D.
5. PREVIOUS DOCUMENTS:

Type	Date	Comments
Original	2010-11-29	Original
IQA	2011-01-11	Comments for filing letter
Filing Issues Identified	2011-02-11	Comments based on IQA
Chem Review #1	2011-04-27	Deficiencies identified
DR Letter	2011-04-28	Comments based on CR #1
Amendment	2011-06-23	Response to DR Letter
Quality Micro Review	2011-08-16	Deficient for lack of testing for <i>Burkholderia cepacia</i>
Chem Review #1 Amendment	2011-08-26	Review of 2011-06-23 amendment
CR Letter	2011-09-28	Not approvable including lack of testing for <i>Burkholderia cepacia</i>

## 6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date	Comment
Complete Response	11/18/2014	Class 2 Resubmission

## 7. NAME & ADDRESS OF APPLICANT AND AGENT:

### Applicant

Name: Mikart Inc  
 Address: 1750 Chattahoochee Ave Northwest  
 Atlanta, Georgia 30318

## 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: FLOWTUSS
- b) Non-Proprietary Name (USAN): Hydrocodone Bitartrate and Guaifenesin Oral Solution
- c) Chem. Type/Submission Priority
  - Chem. Type: 4
  - Submission Priority: S

## 9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: opioid analgesic/expectorant

11. DOSAGE FORM: Solution

12. STRENGTH/POTENCY: 2.5 mg hydrocodone bitartrate/200 mg guaifenesin per 5 mL

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:  Rx  OTC

Chemistry Review #2 NDA 22424

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): None

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT: See Chem. Review #1

17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

Reviewed: **ACCEPTABLE**

DMF	Holder	DMF Subject	Review Date
		(b) (4)	Adequate 09/19/2014
			Adequate. IR sent for revised manufacturing process. 04/23/2015

DMFs for packaging materials were not reviewed since there is sufficient information in the NDA  
See Section P.7 Container Closure below

**B. Other Documents:**

18. STATUS:

**CONSULTS/ CMC RELATED REVIEWS:**

- Pharm/Tox consult for (b) (4) genotox studies in DMF (b) (4) **Acceptable** May 22, 2009
- EA waiver requested in 1.12.14. Granted **Acceptable**
- Inspection: All manufacturing and testing sites have been found **Acceptable** on Feb 12, 2015.

**The Chemistry Review for NDA 22424**

**I. Recommendations**

1. Recommendation and Conclusion on Approvability: **The application may be approved from a CMC point of view.** All manufacturing and testing sites have been found Acceptable on Feb 12, 2015.
2. **Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.** None

**II. Summary of Chemistry Assessments**

**A. Description of the Drug Product(s) and Drug Substance(s)**

**1. Drug Substances**

The drug substances, Hydrocodone Bitartrate (HC) and Guaifenesin (GU), are USP items and their properties and synthesis have been assessed many times to support many applications. They are provided by two manufacturers, HC (b) (4) (DMF (b) (4)) and GU (DMF (b) (4)) (b) (4). The DMFs have been recently reviewed and found acceptable.

There had been a concern (b) (4) because this impurity is potentially genotoxic. The pharm/tox evaluation of the information provided by the DMF holder has concluded that this is not an issue of concern and the DMF is now acceptable to support this NDA.

Since the drug product is a solution polymorphism is not an issue.

**2. Drug Product**

The drug product is an oral solution. The manufacturing process and controls are straightforward. All of the excipients are compendial except the colors, which are FD&C and D&C colors, and the flavoring, (b) (4)

The applicant submitted testing and validation for *Burkholderia cepacia*, which was found acceptable in a Microbiology Quality Review dated 12-08/2014.

The drug product is very stable in terms of its chemistry, showing no changes in any of the tested parameters, including degradants, over the 24 months reporting for three batches in the proposed packaging, 4 ounce and 16 ounce plastic bottles. Therefore an expiration period of 24 months is acceptable.

**B. Description of How the Drug Product is Intended to be Used**

The drug product is intended to be used (b) (4)  
(b) (4)  
Each of these drug substances has been approved separately for their labeled uses.

**C. Basis for Approvability or Not-Approval Recommendation**

The CMC for the drug substances are adequately described to provide adequate quality for their intended use.

**III. Administrative**

There have been no changes in the information in the NDA since the first review except an update in the specifications to add a test for *Burkholderia cepacia*. The testing and validation for this determination were found acceptable by the Microbiologist in a review dated 12/08/2014 in DARRTS.

**I. Review of Common Technical Document-Quality (CTD-Q) Module 3.2: Body of Data**

**S DRUG SUBSTANCE [Hydrocodone bitartrate, (b) (4)] ACCEPTABLE See Chem. Review #1 and Amendment**

**S DRUG SUBSTANCE [Guaifenesin, (b) (4)] ACCEPTABLE Chem. Review #1 and Amendment**

**P DRUG PRODUCT**

**P.1 Description and Composition of the Drug Product**

**ACCEPTABLE See Chem. Review #1 and Chem Review #1 Amendment**

**P.2 Pharmaceutical Development: ACCEPTABLE See Chem. Review #1 and Chem Review #1 Amendment**

**P.3. Manufacture ACCEPTABLE See Chem. Review #1 and Chem Review #1 Amendment**

**P.3.1 Manufacturers**

Site	Function	Inspection Status from Panorama	
		Status	Date
Mikart Inc. 12090 Marietta Blvd Atlanta GA 30318 CFN 1050658	Manufacturing	Acceptable	05-Feb-2015
Mikart Inc. 1750 Chattahoochee Ave Atlanta GA 30318 CFN 1050658	Packaging/Labeling		
Mikart Inc. 1595 Chattahoochee Ave Atlanta GA 30318 CFN 1050658	Testing		
(b) (4)	(b) (4)	Acceptable	(b) (4)

**P.3.2 Batch Formula ACCEPTABLE See Chem. Review #1 and Chem Review #1 Amendment**

**P.3.3. Description of Manufacturing Process ACCEPTABLE See Chem. Review #1 and Chem Review #1 Amendment**

**P.3.4. Controls of Critical Steps and Intermediates ACCEPTABLE See Chem. Review #1 and Chem Review #1 Amendment**

**P.4 Control of Excipients ACCEPTABLE See Chem. Review #1 and Chem Review #1 Amendment**

**P.5 Control of Drug Product**

**P.5.1 Specification(s)**

Chemistry Review #2 NDA 22424

Changes from Review #1

1. Color (b) (4) "violet" (b) (4)
2. Added test for *Burkholderia cepacia*, per request in CR letter.
3. Change acceptance criteria for microbial tests

Test	Original	Revised
Total Plate Count (TPC)	NMT (b) (4) CFU	NMT (b) (4) CFU/mL
Total Combined Yeasts and Molds Count	NMT (b) (4) CFU	NMT (b) (4) CFU/mL
<i>Burkholderia cepacia</i>		Absent

These changes are **ACCEPTABLE**

The specifications copied from the application are:

<b>Test</b>	<b>Limits</b>	<b>Method</b>
<i>Appearance</i>	<i>Meets Description (A transparent liquid with a (b) (4) color that has a black raspberry smell. No solid matter is visible.)</i>	<i>Visual</i>
<i>pH</i>	(b) (4)	FPSPG001
<i>Specific Gravity</i>	(b) (4)	FPSPG002
<b>Identification (HPLC Retention Times)</b>		FPSPMF112 0A
- Hydrocodone Bitartrate 2 1/2 Hydrate	<i>Retention time meets standard</i>	
- Guaifenesin	<i>Retention time meets standard</i>	
<b>Assay and Impurities</b>		
- Hydrocodone Bitartrate 2 1/2 Hydrate	(b) (4) %	
- (b) (4)	NMT (b) (4) %	
- Other Individual Impurity	NMT (b) (4) %	
- Total Impurities	NMT (b) (4) %	
<b>Guaifenesin</b>		
- (b) (4)	(b) (4)	
- (b) (4)	NMT (b) (4) %	
- (b) (4)	NMT (b) (4) %	
- Other Individual Impurity	NMT (b) (4) %	
- Total impurities	NMT (b) (4) %	
<b>Methylparaben</b>		
(b) (4)	(b) (4) %	
<b>Propylparaben</b>		
(b) (4)	(b) (4) %	
<b>Microbiological Testing</b>		
- Total Plate Count (TPC)	NMT (b) (4) CFU/mL	
- Total Combined Yeasts and Molds Count	NMT (b) (4) CFU/mL	
- <i>E. Coli</i>	<i>Absent</i>	
- <i>Burkholderia cepacia</i>	<i>Absent</i>	

**ACCEPTABLE**

**P.5.2 Analytical Procedures ACCEPTABLE See Chem. Review #1 and Chem Review #1 Amendment and Amendment**

**P.5.3 Validation of Analytical Procedures ACCEPTABLE See Chem. Review #1 and Chem Review #1 Amendment**

**P.5.4 Batch Analysis ACCEPTABLE See Chem. Review #1 and Chem Review #1 Amendment**

**P.5.5. Characterization of Impurities ACCEPTABLE See Chem Review #1**

**P.5.6 Justification of Specification(s) ACCEPTABLE See Chem. Review #1 and Chem Review #1 Amendment**

**P.6 Reference Standards or Materials ACCEPTABLE See Chem. Review #1 and Chem Review #1 Amendment**

**P.7 Container Closure System: ACCEPTABLE See Chem. Review #1 and Chem Review #1 Amendment**

**P.8 Stability**

**P.8.1 Stability Summary and Conclusions** The data support the proposed expiration date of 24 months in the 4 ounce and 16 ounce bottles. **ACCEPTABLE**

**P.8.2 Post-approval Stability Protocol and Stability Commitment ACCEPTABLE See Chem. Review #1 and Chem Review #1 Amendment**

**CHECK**

**P.8.3 Stability Data** The applicant has provided the results of stability testing for up to 24 months for lots manufactured at their facility in Atlanta GA. All batches remained well within specifications. **ACCEPTABLE**

**A APPENDICES N/A**

**R REGIONAL INFORMATION**

**R1 Executed Batch Records. ACCEPTABLE**

**R2 Comparability Protocol N/A**

**R3 Methods Validation Package N/A**

**II. LABELING ACCEPTABLE See Chem. Review #1 and Chem Review #1 Amendment**

**Comments to be Communicated to Applicant: None**

**NDA 22-424****Flowtuss  
(Hydrocodone Bitartrate and Guaifenesin)  
Oral Solution****Tiber Laboratories, LLC****Xiaobin Shen, Ph.D.  
for  
Division of Pulmonary, Allergy and Rheumatology Drug  
Products**

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# Chemistry Review Data Sheet

1. NDA 22-424
2. REVIEW #: 1 Amendment
3. REVIEW DATE: 25-Aug-2011
4. REVIEWER: Xiaobin Shen, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original	21-Sept-2010
Amendment 0001	06-Jan-2011
Amendment 0002	22-Feb-2011
Chemistry review 1	26-Apr-2011

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment 0003	14-Apr-2011
Amendment 0004	15-May-2011
Amendment 0007*	23-Jun-2011

\* Other amendments submitted prior to Amendment 0007 do not have CMC information.

7. NAME & ADDRESS OF APPLICANT:

Name: Tiber Laboratories, LLC  
Address: 5400 Laurel Springs Parkway, Suite 803  
Suwanee, GA 30024  
Representative: Cassie Vitolo, Director, Regulatory Affairs  
Telephone: (678) 208-0388

## Chemistry Review Data Sheet

Facsimile: (678) 208-0346

**8. DRUG PRODUCT NAME/CODE/TYPE:**

- a) Proprietary Name: Flowtuss
- b) Non-Proprietary Name (USAN): Hydrocodone Bitartrate and Guaifenesin oral solution
- c) Code Name/# (ONDQA only): N/A
- d) Chem. Type/Submission Priority (ONDQA only):
  - Chem. Type: 4
  - Submission Priority: S

**9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)**

The application is filed based on previously approved NDA and existing OTC monographs listed below:

Hydrocodone Bitartrate — Hycomine Syrup, 5 mg/5 mL, NDA 19-410; Hycodan Tablets and Syrup, 5 mg/tablet and 5 mg/5 mL, NDA 05-213.

Guaifenesin — OTC monograph for expectorant drug products, 21 CFR 341.18.

**10. PHARMACOL. CATEGORY:**

Hydrocodone bitartrate is antitussive (cough suppressing); Guaifenesin is an expectorant.

**11. DOSAGE FORM: Oral Solution****12. STRENGTH/POTENCY: 2.5 mg Hydrocodone Bitartrate, and 200 mg Guaifenesin per 5 mL.****13. ROUTE OF ADMINISTRATION: Oral**

14. Rx/OTC DISPENSED:  Rx  OTC

**15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):**

SPOTS product – Form Completed

Not a SPOTS product

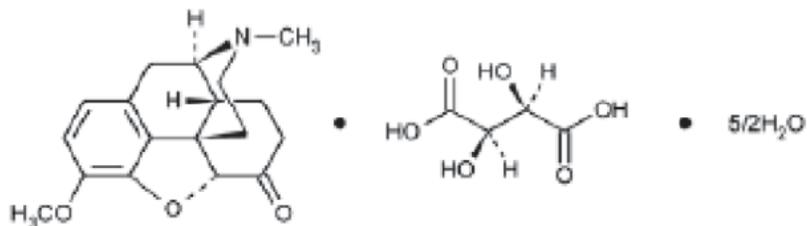
## Chemistry Review Data Sheet

## 16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

There are two active pharmaceutical ingredients in this product.

Hydrocodone Bitartrate:

4,5 $\alpha$ -Epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5)

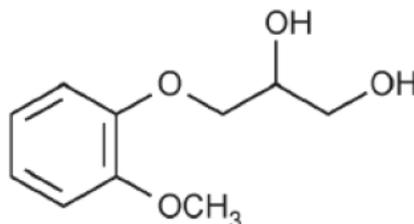


Molecular Formula: C<sub>18</sub>H<sub>21</sub>NO<sub>3</sub>·C<sub>4</sub>H<sub>6</sub>O<sub>6</sub>·2½H<sub>2</sub>O

Molecular Weight: 494.490

Guaifenesin:

(±)-3-(o-Methoxyphenoxy)-1,2-propanediol



Molecular Formula: C<sub>10</sub>H<sub>14</sub>O<sub>4</sub>

Molecular Weight: 198.22

## 17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	27-Jul-2011	NA
	II			3	Adequate	20-Dec-2010	NA

Chemistry Review Data Sheet

(b) (4)		(b) (4)				
	III		4	NA	NA	NA
	III		4	NA	NA	NA
	III		4	NA	NA	NA
	III		4	NA	NA	NA
	III		4	NA	NA	NA
	III		4	NA	NA	NA
	III		4	NA	NA	NA
	III		4	NA	NA	NA

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NA	NA	NA

Chemistry Review Data Sheet

18. STATUS:

**ONDQA:**

<b>CONSULTS/ CMC RELATED REVIEWS</b>	<b>RECOMMENDATION</b>	<b>DATE</b>	<b>REVIEWER</b>
Biometrics	NA	NA	NA
EES	Acceptable	27-Jul-2011	NA
Pharm/Tox	Approval	21-Jul-2011	Dr. Grace S. Lee
Biopharm	NA	NA	NA
<b>LNC</b>	<b>Pending</b>	<b>25-Aug-2011</b>	
Methods Validation	Validation is not required by FDA Lab	17-Mar-2011	Dr. Xiaobin Shen
EA	Acceptable	17-Mar-2011	Dr. Xiaobin Shen
Microbiology	Approvable (pending resolution of microbiology deficiencies)	16-Aug-2011	Dr. John W. Metcalfe

# The Chemistry Review for NDA 22-424

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls standpoint, the NDA is approvable with a 24 month expiry pending satisfactory resolution of the microbiology related deficiencies.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

No post-marketing items.

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Substance(s) and Drug Product(s)

##### Drug substances

There are two drug substances in this NDA: hydrocodone bitartrate and guaifenesin.

1- Hydrocodone is a semi synthetic narcotic antitussive and analgesic. It exists in fine white crystals or crystalline powder. It is soluble in water and slightly soluble in alcohol. The hydrocodone bitartrate drug substance is manufactured (b) (4) per DMF (b) (4) which was last reviewed in July, 2011 by this reviewer and deemed adequate. The DMF's facility's EES status is acceptable. The release specifications for hydrocodone bitartrate comply with the USP monograph and ICH Q3A and include appearance, identification, specific rotation, pH, loss on drying, residue on ignition, chloride, (b) (4) impurities, assay, related substances (specified and unspecified), and residual solvents. This drug substance is packaged (b) (4). Its stability data is referenced to DMF (b) (4) which supports the claimed retest period of (b) (4) months.

2- Guaifenesin is an expectorant. It exists as white or off-white crystalline powder. It is odorless or has a slightly characteristic odor. It is soluble in water. The guaifenesin drug substance is manufactured (b) (4) per DMF (b) (4) which was last reviewed in September, 2008 by Dr. Yong-De Lu and deemed adequate. The subsequent amendments were reviewed by Dr. Arthur Shaw last in December, 2010, since then no technical amendments have been made to the DMF by 27-Jul-2011, the DMF remains adequate. The DMF's facility's EES status is acceptable. The release specifications for guaifenesin comply with the USP monograph and ICH Q3A and include appearance, identification, melting range, loss on drying, heavy metal, assay and impurities. This drug substance is packaged (b) (4).

## Chemistry Assessment Section

(b) (4) Its stability data is referenced to DMF (b) (4) which supports the claimed retest period of (b) (4) months.

**Drug product**

The drug product, hydrocodone bitartrate and guaifenesin oral solution with the trade name as Flowtuss, is a (b) (4) liquid with a black raspberry aroma. It is indicated for (b) (4)

Each 5 mL of the oral solution contains 2.5 mg of hydrocodone bitartrate, and 200 mg of guaifenesin. In addition to the two active pharmaceutical ingredients, it also contains sorbitol, glycerin, saccharin sodium, polyethylene glycol (b) (4) methylparaben, propylparaben, citric acid, sodium citrate, (b) (4) black raspberry flavor, FD&C Blue #1 colorant, D&C Red # 33 colorant, and water as excipients. These excipients are commonly used in oral solution products. The product is packaged into both 4 oz and 16 oz HDPE bottles and closed with child resistant caps.

The drug product is manufactured by Mikart, Inc. at Atlanta, GA. This facility's EES status is acceptable. The drug product release specifications include appearance, pH, specific gravity, identification, assay, (b) (4) impurity, (b) (4) and microbial limits. The stability study was conducted on 3 manufacturing batches for registration. All 3 batches were packaged into the 16 oz HDPE bottles and tested for stability. One of the batch was also packaged into the 4 oz HDPE bottles and tested for stability. Up to 36 months of stability study at real time is planned, up to 12 months of real time and full 6 months of accelerated stability data are provided. The provided data show no meaningful change in all tested product quality attributes beyond typical analytical variations. Based on ICH Q1E, the provided data support an expiry of 24 months claimed by the applicant.

**B. Description of How the Drug Product is Intended to be Used**

The drug product hydrocodone and guaifenesin oral solution is packaged in 4 and 16 fl. oz HDPE bottles. Each 5 mL of the oral solution contains 2.5 mg of hydrocodone bitartrate and 200 mg guaifenesin.

(b) (4)  
The manufacturer proposed a two year expiry with 20 C to 25 C storage condition, the firm provided 12 month real time stability data to support the two year expiry and it is acceptable.

**C. Basis for Approvability or Not-Approval Recommendation**

The NDA submission and amendments provided acceptable information on the chemistry, manufacturing, and controls of the hydrocodone and guaifenesin oral solution. The product is recommended for approval, upon resolution of the microbiology related deficiencies, based on the following:

### Chemistry Assessment Section

- The drug substance and product specifications provide adequate controls;
- The drug product excipients are of USP/NF grade or have been evaluated and deemed acceptable;
- The drug product container closure systems are acceptable for pharmaceutical use;
- Both drug substance and drug product are stable in the studied stability period and support 24 months of drug product expiry.

### III. Administrative

#### A. Reviewer's Signature

Chemist: Xiaobin Shen, Ph.D. *{Signed electronically in DARRTS}*

#### B. Endorsement Block

ChemistName/Date:

ChemistryTeamLeaderName/Date:

ProjectManagerName/Date:

#### C. CC Block

## Chemistry Assessment Section

**Chemistry Assessment****I. Review of Quality Information Amendment 0003 (14-Apr-2011)**

Amendment 0003 is a response to pharmacology/toxicology reviewer's Dr. Grace Lee's information request on 05-Apr-2011. This response has been reviewed by Dr. Grace Lee.

**II. Review of Quality Information Amendment 0004 (15-May-2011)**

Amendment 0005 is a response to information request in the 11-Feb-2011 filing communication. Only CMC related responses are evaluated in this chemistry review.

**Point-by Point Responses****Information Request 2**

*Provide methods validation data for relevant non-compendial methods (e.g., chromatographic methods, microbiological assays) as per the ICH Q2A and Q2B guidances.*

**Applicant Response**

A revised Module 3.2.R Regional R1 is provided along with the following methods validation documents:

3.2.R.3.P.3 - Attachment 3a [for Guaifenesin]

3.2.R.3.P.4 - Attachment 3b

3.2.R.3.P.5 - Attachment 2a [for Hydrocodone Bitartrate]

3.2.R.3.P.6 - Attachment 2b

3.2.R.3.P.7 - Attachment 5a [for Methylparaben and Propylparaben]

3.2.R.3.P.8 - Attachment 5b

**Evaluation:** Adequate. Each of the provided attachment is separately evaluated below.

3.2.R.3.P.3 - Attachment 3a [for Guaifenesin]: The applicant labeled it wrong, this section should be for Hydrocodone Bitartrate]

The applicant validated the following method attributes and provided alongside the validation results —

*Start of Sponsor Material*

---

Chemistry Assessment Section

Method Verification Parameter	Number
(b) (4) Study	Expt. 1
Specificity	Expt. 2
Forced Degradation (Stress Study)	Expt. 3
Linearity	Expt. 4
Accuracy and Precision	Expt. 5
System Precision	Expt. 6
(b) (4) Precision - (b) (4)	Expt. 7
Precision - (b) (4)	Expt. 8
Solution Stability	Expt. 9
LOD and LOQ	Expt. 10
Robustness	Expt. 11

**3.4 Results Summary Table**

Method Validation Parameter	Results
System Precision	For runs to considered valid all system suitability parameters were met, see section 9.0 for results summary.
(b) (4)	(b) (4)
Accuracy and Precision	(b) (4)
Linearity	
LOD and LOQ	
(b) (4)	
Precision- (b) (4)	
(b) (4) Precision- (b) (4)	
Solution Stability	
Robustness	
Specificity and Forced Degradation	

*End of Sponsor Material*

Note that the forced degradation studies were conducted on both drug substance and drug product.

The robustness study validated (b) (4)

## Chemistry Assessment Section

The provided validation results support that the method is suitable for the assay and impurity analysis for hydrocodone bitartrate in the drug product.

3.2.R.3.P.4 - Attachment 3b

This attachment is the notebook record for content of 3.2.R.3.P.3. No particular assessment is necessary.

3.2.R.3.P.5 - Attachment 2a [for Hydrocodone Bitartrate: The applicant labeled it wrong, should be for Guaifenesin]

The applicant validated the following method attributes and provided alongside the validation results —

*Start of Sponsor Material*

---

Method Verification Parameter	Number
(b) (4) Study	Expt. 1
Specificity	Expt. 2
Forced Degradation (Stress Study)	Expt. 3
Linearity	Expt. 4
Accuracy and Precision	Expt. 5
System Precision	Expt. 6
(b) (4) Precision - (b) (4)	Expt. 7
Precision - (b) (4)	Expt. 8
Solution Stability	Expt. 9
LOD and LOQ	Expt. 10
Robustness	Expt. 11

Chemistry Assessment Section

**3.6 Results Summary Table**

Method Validation Parameter	Results
System Precision (b) (4)	For runs to considered valid all system suitability parameters were met, see section 9.0 for results summary. (b) (4)
Accuracy and Precision	(b) (4)
Linearity	
Precision- (b) (4)	
Precision- (b) (4)	
Precision- (b) (4)	
Solution Stability	
Robustness	
Specificity and Forced Degradation	

*End of Sponsor Material*

Not that the forced degradation studies were conducted on both drug substance and drug product.

The robustness study validated (b) (4)

The provided validation results support that the method is suitable for the assay and impurity analysis for guaifenesin in the drug product.

3.2.R.3.P.6 - Attachment 2b

This attachment is the notebook record for content of 3.2.R.3.P.5. No particular assessment is necessary.

3.2.R.3.P.7 - Attachment 5a [for Methylparaben and Propylparaben]

The applicant validated the following method attributes and provided alongside the validation results —

*Start of Sponsor Material*

## Chemistry Assessment Section

Method Verification Parameter	Number
(b) (4) Study	Expt. 1
Specificity	Expt. 2
Specificity - Forced Degradation (Stress Study)	Expt. 3
Linearity	Expt. 4
Accuracy and Precision - Finished Product	Expt. 5
Accuracy and Precision - Raw Material	Expt. 5A
System Precision	Expt. 6
(b) (4) Precision - Finished Product (b) (4)	Expt. 7
Precision - Finished Product	Expt. 8
Precision - Raw Material (b) (4)	Expt. 7A
Precision - Raw Material	Expt. 8A
Solution Stability	Expt. 9
Robustness	Expt. 10

Method Validation Parameter	Results
System Precision	For all runs to considered valid all system suitability parameters were met, see section 9.0 for results summary.
(b) (4)	(b) (4)
Accuracy and Precision	(b) (4)
Linearity	
(b) (4)	
Precision	
(b) (4)	
Precision-	
(b) (4)	
Solution Stability	
Robustness	
Specificity and Forced Degradation	

*End of Sponsor Material*

Not that the forced degradation studies were conducted on both drug substance and drug product.

## Chemistry Assessment Section

The robustness study validated [REDACTED] (b) (4)

The provided validation results support that the method is suitable for the assay and impurity analysis for methylparaben and propylparaben in the drug product.

**3.2.R.3.P.4 - Attachment 5b**

This attachment is the notebook record for content of 3.2.R.3.P.7. No particular assessment is necessary.

**Information Request 3**

Provide for each batch of [REDACTED] (b) (4) colors (Blue #1, Red #33) used to make the NDA batches an FDA certificate of batch certification.

**Applicant Response**

The certificates of analysis for Blue #1 and Red #33 were provided in Module 3.2.P.4 Control of Excipients.

**Evaluation:** Adequate. The CoAs were located and deemed acceptable.

**Information Request 4**

Since the drug formulation contains significant levels of excipients [REDACTED] (b) (4) [REDACTED] provide data and controls for container closure component extractables [REDACTED] (b) (4) and for leachables [REDACTED] (b) (4)

Alternatively, provide a data based justification for a lack of controls for extractables and leachables. For any extractables and leachables which were identified, provide a safety assessment of such extractables and leachables.

**Applicant Response**

Mikart performed and submitted USP <661> extractable substances and heavy metals testing for each CC system. Results were submitted in the following subsection of the original NDA submission:

**3.2.P.7.4 USP Testing Results**

USP testing is performed for each proposed container/closure system the first time it is received by Mikart. [REDACTED] (b) (4)

[REDACTED] This section contains the following information:

## Chemistry Assessment Section

- USP Test Results [REDACTED] (b) (4)  
(Refer to Attachment 3.2.P.7.4.1, original submission)  
[REDACTED] (b) (4)  
Information on [REDACTED] (b) (4) utilized in this application, is included in previous sections.

The sample is in compliance with the requirements for the tests conducted.

- USP Test Results [REDACTED] (b) (4)  
(Refer to Attachment 3.2.P.7.4.2, original NDA submission)  
[REDACTED] (b) (4)  
Information on [REDACTED] (b) (4) utilized in this application, is included in previous sections.

The sample is in compliance with the requirements for the tests conducted.

[REDACTED] (b) (4)

[REDACTED] (b) (4) data sheets submitted in the NDA original submission specified compliance with 21 CFR [REDACTED] (b) (4) and based on proposed indications, an acute dosing regimen would be utilized by the patient.

**Evaluation:** Acceptable. The justifications are acceptable. [REDACTED] (b) (4)

[REDACTED]

**Information Request 5**

*Provide 100% size color mockups of each actual carton and immediate container label.*

## Chemistry Assessment Section

**Applicant Response**

Labeling deficiencies included in this letter were addressed in Submission 0002 dated February 22, 2011.

**Evaluation:** Acceptable. The sponsor updated the carton and container label files. N

**Information Request 6**

*Clarify that the formulation of drug product used for the clinical/bio studies was the same as that proposed for marketing.*

**Applicant Response**

As referenced in Section 2.2 Introduction (pages 2 & 3), Section 2.5 Clinical Overview (page 6) – all state that the 3-ingredient product was used in the bio study, but provides formulation information to justify the use of the data for approval of the 2-ingredient product.

**Evaluation:** Acceptable. The only difference is that the 3-ingredient product has the pseudoephedrine hydrochloride.

**Information Request 7**

*Clarify the specifications for the drug product in section 3.2.P.5.1, which contains an assay for pseudoephedrine hydrochloride and its impurities. This appears to be an error.*

**Applicant Response**

A revised Section 3.2.P.5.1 Specification R1 is provided in this amendment.

**Evaluation:** Acceptable. The pseudoephedrine hydrochloride related entries are removed.

**Information Request 8**

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

**Applicant Response**

The Microbial Limits testing is performed per USP <61> and <62>. Validation of compendial methods is not required.

Regarding [REDACTED] (b) (4) that was performed [REDACTED] (b) (4) [REDACTED] according to USP methods, the following documents are provided:

## Chemistry Assessment Section

- 3.2.P.2.2 SOP [REDACTED] (b) (4)
- 3.2.P.2.3 Prep Test Validation - [Preparatory Testing (Validation) of the USP  
[REDACTED] (b) (4) Summary of Test  
Results]
- 3.2.P.2.4 SOP [REDACTED] (b) (4)
- 3.2.P.2.5 SOP 147 - (Suitability Determination in the Presence of the Product for Total Aerobic Microbial Count Test, Total Yeasts and Mild Count Test, Absence of Salmonella spp. and E. coli, and Staphylococcus aureus)
- 3.2.P.2.6 USP 32 Suitability Test Data

**Evaluation:** Acceptable from CMC perspective. Microbiologist Dr. John W. Metcalfe has evaluated the submitted information and concluded that the application is approvable pending resolution of microbiology deficiencies. Two microbiology deficiencies have been identified. Refer to Dr. Metcalfe's microbiology review completed on 16-Aug-2011 for details.

**Information Request 9**

*We note that the proposed shelf life is 24 months even though you have provided [REDACTED] (b) (4) months of real time data. As per the ICH Q1A guidance, a maximum of [REDACTED] (b) (4) months shelf life may be granted provided the stability data are robust."*

**Applicant Response**

A revised Section 3.2.P.8.3 Stability Data R1 is provided in this amendment, along with the stability report, 3.2.P.8.3.19 Stability Data 9 Mo.

**Evaluation:** Acceptable. Additional stability data is submitted in Amendment 0007 (23-Jun-2011), the new stability data in both amendments are evaluated below.

**III. Review of Quality Information Amendment 0007 (23-Jun-2011)**

Amendment 0007 is a response to deficiencies and information requests in the 28-Apr-2011 CMC Discipline Review Letter.

**Point-by Point Responses****Information Request 1**

*The guaifenesin drug substance impurity limits that you transcribed from guaifenesin USP monograph do not incorporate [REDACTED] (b) (4) this is misleading. Amend your impurity analysis method to include [REDACTED] (b) (4) in the impurity result calculation. Also update the guaifenesin drug substance specification table with the corrected drug substance impurity specifications, which are also modified in consideration of ICH Q3A.*

## Chemistry Assessment Section

**Applicant Response**

USP was contacted and it was confirmed that the monograph formula, (b) (4) is correct. The monograph calculation relies on (b) (4)

(b) (4) As a result, no changes to the method are required; however, the impurity specifications have been revised as requested. Please refer to the response to item #2 below.

**Evaluation:** Acceptable. Additional stability data is submitted in Amendment 0007 (23-Jun-2011), the new stability data in both amendments will be reviewed together.

**Information Request 2**

*The guaifenesin drug substance specifications for other individual impurities do not meet ICH Q3A requirements. Tighten the specification limits by considering both ICH Q3A recommendations and test results.*

**Applicant Response**

Mikart (the drug product manufacturer) has revised the impurity specifications by reporting known and unknown impurities separately. This change is made to comply with the recommendations in the ICH Q3A guidance. With this segregation, the limit for unknown impurities has been tightened to NMT (b) (4)% in accordance with the guidance. Please see the included electronic specification and test procedure files for Guaifenesin raw material code (b) (4), as follows:

**Module 3.2.S Drug Substance - Guaifenesin**

3.2.S.4.1.1 mikart specifications R1

3.2.S.4.2.1 mikart analytical procedures R1

**Evaluation:** Acceptable.

**Information Request 3**

*Drug product manufacturing process related comments are listed below.*

a) (b) (4)

**Applicant Response**

The process flow diagram and master packaging records (4 oz and 16 oz) have been revised (b) (4) Please see the included electronic files for the drug product as follows:

## Chemistry Assessment Section

**Module 3.2.P Drug Product**

3.2.P.3.3.1 Manufacturing Flow Diagram R1

3.2.P.3.3.3 master pkg 4oz R1

3.2.P.3.3.4 master pkg 16oz R1

**Evaluation:** Adequate.

b)

(b) (4)

*Clarify this hold duration time limit in the manufacturing process section and master batch record.*

**Applicant Response**

Information regarding hold times for bulk product solution was included in the original application in section **3.2.P.3.4 Control of Critical Steps and Intermediates**. In this section, it is specified

(b) (4)

Since this hold time is specified within Mikart's internal Standard Operating Procedures, the master batch record would only be annotated if a hold time <sup>(b) (4)</sup> is required.

**Evaluation:** Acceptable.

c) *Provide product stability and microbial limit data to support your maximum product solution hold duration.*

**Applicant Response**

After packaging is completed, each lot of Hydrocodone Bitartrate and Guaifenesin Oral Solution is subjected to complete analysis according to the finished product test specification sheet presented in section **3.2.P.5.1 Control of Drug Product - Specifications**. This testing includes microbial analysis. As a result of this routine finished product testing, every batch hold-time is evaluated and no additional testing is necessary.

## Chemistry Assessment Section

Review of the executed records revealed that the hold times for the exhibit batches were as follows:

(b) (4)

Review of the Certificates of Analysis for each of the above exhibit batches reveals (b) (4)

(b) (4) Please refer to the original application, section 3.2.P.5.4 Control of Drug Product – Batch Analysis, for additional information.

**Evaluation:** Acceptable.

**Information Request 4**

Provide the (b) (4) release testing requirements for all excipients. At least an identification test is required if the excipient is accepted on the basis of a Certificate of Analysis and is used within its retest period.

**Applicant Response**

Mikart does not accept any of the materials solely on the basis of a Certificate of Analysis. A summary of Mikart's (b) (4) release testing program for each excipient was presented in the original application within section 3.2.P.4.1 Control of Excipients - Specifications.

Following vendor qualification, the tests listed under the heading (b) (4)

The remaining tests listed on the specification sheets are performed (b) (4)

**Evaluation:** Adequate.

**Information Request 5**

Drug product release and stability specifications related comments are listed below.

- a) The specifications table has acceptance criteria for pseudoephedrine, which is not a component of this product. Update the specification table to remove the entry.

**Applicant Response**

The inclusion of the pseudoephedrine in the table was a typographical error that has since been addressed in Amendment 0004 (dated 5/16/11), Response to item 7 of the Agency's Filing Communication (dated 02/11/11).

**Evaluation:** Adequate.

## Chemistry Assessment Section

- b) *There is only one identification test for each drug substance. Include a complementary identification test.*

**Applicant Response**

A complementary UV identification test has been added for each active ingredient in the drug product formulation. Please see the included electronic files for finished product specifications and the corresponding test procedure.

**Evaluation:** Adequate.

- c) *Add a deliverable volume test to the product at 4 oz package configuration. USP <698> requires this test when the product is labeled to contain not more than 250 mL.*

**Applicant Response**

The deliverable volume test applicable to the 4 oz package configuration has been added to the release testing requirements.

**Evaluation:** Adequate.

- d) *The drug product impurity acceptance criteria should follow ICH Q3B. At the proposed total daily dose for both hydrocodone and guaifenesin, impurities not less than (b)(4)% should be identified, impurities not less than (b)(4)% should be qualified. The acceptance criteria of NMT (b)(4)% for any other individual impurity is not acceptable if there are unidentified impurities in this category. We recommend you to segregate the identified and unidentified impurities and establish the corresponding acceptance criteria in reference to ICH Q3B. Impurities in the drug product not less than (b)(4)% should be qualified.*

**Applicant Response**

Mikart has revised the drug product impurity specifications by reporting known and unknown impurities separately. This change is made to comply with the recommendations in the ICHQ3B guidance. With this segregation, the limit for unknown impurities has been tightened to NMT (b)(4)% in accordance with the guidance.

**Evaluation:** Adequate.

- e) *The total combined molds and yeasts count acceptance criterion of NMT (b)(4) CFU for the drug product is (b)(4) the USP <1111> recommended limit of NMT 20 cfu/g or mL for aqueous oral solution. Tighten the limit.*

## Chemistry Assessment Section

**Applicant Response**

Mikart has tightened the limit for Total Combined Molds and Yeast to NMT (b) (4) cfu/mL (b) (4)

**Evaluation:** Adequate.

*f) Conduct forced degradation studies of the drug product to identify potential degradants in reference to the known drug substance related impurities and degradants.*

**Applicant Response**

Forced degradation studies were submitted in Amendment 0004 (dated 5/16/11), Response to item 2 of the Agency's Filing Communication (dated 02/11/11).

**Evaluation:** Adequate.

**Information Request 6**

*Clarify if the original method used by Propharma to analyze hydrocodone and guaifenesin in the drug product was ever validated. Provide the original method validation report, or validate it per ICH Q2 (R1).*

**Applicant Response**

Method validation studies for hydrocodone and guaifenesin in the drug product were submitted in Amendment 0004 (dated 5/16/11), Response to item 2 of the Agency's Filing Communication (dated 02/11/11).

**Evaluation:** Adequate. The provided method validation information are evaluated on page 11 on this review and deemed adequate.

**Information Request 7**

*Provide a validation report for the method used to analyze methylparaben and propylparaben in the drug product. The validation should be conducted per ICH Q2 (R1).*

**Applicant Response**

Method validation studies for methylparaben and propylparaben in the drug product were submitted in Amendment 0004 (dated 5/16/11), Response to item 2 of the Agency's Filing Communication (dated 02/11/11).

**Evaluation:** Adequate.

**Information Request 8**

## Chemistry Assessment Section

*Provide representative chromatograms for related substance analysis for hydrocodone and guaifenesin in the drug product with appropriate zoom level to show adequate peak separation and proper integration. Address the following comments. The hydrocodone related substance chromatograms provided along with the batch analysis results are too crowded to identify individual peaks (b) (4)*

*The guaifenesin related substance chromatogram has a unknown and placebo peak crowded together (b) (4). It is not clear if the peaks are adequately separated.*

**Applicant Response**

The chromatograms have been reprinted at an increased zoom level in order to show adequate peak separation and proper integration. The Agency's comments regarding crowding, scale and visibility issues are resolved through the submission of set-scaled fields showing different timed intervals over the entire runtime of each injection. Please see the included electronic document containing the reprinted chromatograms, as follows:

## 3.2.P.5.4.14 Zoomed Chromatograms

**Evaluation:** Adequate. The provided chromatograms demonstrated acceptable peak separation and integration.

**Information Request 9**

*Provide example chromatograms for the analysis of (b) (4) (methylparaben and propylparaben) in the drug product.*

**Applicant Response**

Example chromatograms for the analysis of (b) (4) the drug product were submitted in the original application as follows:

## 3.2.P.5.4.13 (b) (4) Chromatograms (b) (4)

**Evaluation:** Adequate.

**Information Request 10**

*The provided stability data only support (b) (4) months expiry per ICH Q1E. Provide at least 12 month real time stability data to support the proposed two year shelf life.*

**Applicant Response**

Mikart is providing 12 Month stability data for the three (3) registration batches, as requested. Please refer to the included electronic file, as follows:

**Module 3.2.P Drug Product**

## 3.2.P.8.3.20 Stability Data 12 Month Summary

## Chemistry Assessment Section

**Evaluation:** Adequate. The additional stability data (9 Month and 12 Month) submitted after the original submission are evaluated below.

Additional stability data for 9 month and 12 month, stored at the long term conditions of  $25\pm 2^{\circ}\text{C}$  and  $60\pm 5\%$  RH [REDACTED] <sup>(b) (4)</sup> showed no meaningful change in any of the quality attributes tested. All data met and are well within the established specifications. The storage orientation and packaging presentation ( 4 and 16 fl. oz.) have no observed effect on the tested product quality attributes.

The provided 12 month long term stability data is adequate to support a 24 month expiry.

In the CMC discipline review letter the Agency requested the applicant to revise impurity and total combined mold/yeast count reporting acceptance criteria, the applicant responded in this amendment and agreed and have revised it in most of the submission except the stability data table.

**Comment:** Update the revised acceptance limits for impurities and Total Combined Mold/Yeast Count in the stability data summary table in your next stability data update.

**Information Request 11**

*Provide test method(s) for detection and quantification of container closure leachables [REDACTED] <sup>(b) (4)</sup> along with appropriate validation information.*

**Applicant Response**

Information regarding the rationale for exclusion of this testing was submitted in Amendment 0004 (dated 5/16/11), Response to item 4 of the Agency's Filing Communication (dated 02/11/11).

**Evaluation:** Adequate. This issue has been resolved in the evaluation of Amendment 0004 on page 16 of this review.

**Information Request 12**

*Clarify if the drug product manufacturing process is the same or equivalent to that used to manufacture the drug product for the clinical studies. Otherwise clarify the differences.*

**Applicant Response**

The following clarifying information regarding the drug product utilized in the clinical studies was submitted in Amendment 0004 (dated 5/16/11), Response to item 6 of the Agency's Filing Communication (dated 02/11/11).

As referenced in Section 2.2 Introduction R1 (pages 2 & 3), Section 2.5 Clinical Overview R1 (page 6) – all state that the 3-ingredient product was used in the bio study, but provides

## Chemistry Assessment Section

formulation information to justify the use of the data for approval of the 2-ingredient product.

**Evaluation:** Adequate. This issue has been resolved in the review of Amendment 0004.

**Information Request 13**

*The CAS registry number provided for hydrocodone bitartrate drug substance is for the anhydrous form. The CAS registry number for the hydrated form is 34195-34-1. Correct the CAS registry number.*

**Applicant Response**

The correction to the CAS registry number has been made to section 3.2.S.1.1 Nomenclature.

**Evaluation:** Adequate.

**Information Request 14**

(b) (4) requires that (b) (4) on the product label; update the label accordingly.

**Applicant Response**

As requested, (b) (4) has been added to the main display panel of each label.

**Evaluation:** Adequate.

**Information Request 15**

*In the Description section of the package insert, list the components of the oral solution in alphabetical order.*

**Applicant Response**

As requested, the listing of components has been reorganized in the insert such that they appear alphabetically.

**Evaluation:** Adequate.

## Chemistry Assessment Section

### VI. Drug Product Release and Stability Specifications for Commercial Batches

#### Release Specifications



FINISHED PRODUCT SPECIFICATIONS/SUBMISSION FORM

PAGE 1 OF 2

PRODUCT NAME: HYDROCODONE BITARTRATE AND GUAIFENESIN ORAL SOLUTION		MF #: 1120	
STRENGTH: 2.5 mg/200 mg per 5 mL		(A)NDA #: 22-424	
PRODUCT DESCRIPTION			
LIQUID	TABLET	COATED TABLET	CAPSULE
COLOR: (b) (4) AROMA: Black 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)

LOT NO.: _____	SIZE: _____	MIKART DEA #PM0142137, #RM0374203, #RM0197497	
QUANTITY SUBMITTED: _____	DATE: _____	BY: _____	
SUBMITTED TO: _____		ATTN: _____	
DESIGNATED TESTING FACILITY	TEST PROCEDURE	MINIMUM QUANTITY REQUIRED	
MIKART, INC.	FPSPMF1120A FPSPMF1120A - DELIVERABLE VOLUME	16 FL. OZ. 30 BOTTLES	
(b) (4) MIKART	(b) (4)	4 FL. OZ. (b) (4)	

#### SPECIFICATIONS/RESULTS

TEST	LABEL CLAIM	LIMITS	RESULTS	DATE/DONE BY
APPEARANCE		A transparent liquid with a (b) (4) color that has a black raspberry smell		
pH		(b) (4)		
SPECIFIC GRAVITY				
IDENTIFICATION A HYDROCODONE BITARTRATE GUAIFENESIN METHYLPARABEN PROPYLPARABEN		RT's compare to standard		
IDENTIFICATION B: HYDROCODONE BITARTRATE		The UV spectrum of the Hydrocodone Bitartrate peak in the Assay std, generated on a PDA detector, corresponds with the UV spectrum of the Assay Sample Prep		
IDENTIFICATION B: GUAIFENESIN		The UV spectrum of the Guaifenesin peak in the Assay std, generated on a PDA detector, corresponds with the UV spectrum of the Assay Sample Prep		
ASSAY: HYDROCODONE BITARTRATE	2.5 mg per 5 mL	(b) (4)		
IMPURITIES (b) (4) INDIVIDUAL KNOWN IMPURITIES INDIVIDUAL UNKNOWN IMPURITIES TOTAL				
ASSAY: GUAIFENESIN	200 mg per 5 mL			

## Chemistry Assessment Section



FINISHED PRODUCT SPECIFICATIONS/SUBMISSION FORM

PAGE 2 OF 2

PRODUCT NAME: HYDROCODONE BITARTRATE AND GUAIFENESIN ORAL SOLUTION STRENGTH: 2.5 mg/200 mg per 5 mL		MF #: 1120 (A)NDA #: 22-424	
PRODUCT DESCRIPTION			
<b>LIQUID</b>  COLOR: (b) (4) AROMA: Black Raspberry	<b>TABLET</b>  COLOR: SHAPE: DEBOSS: SIDE A: SIDE B: WEIGHT PER UNIT:	<b>COATED TABLET</b>  COLOR: COATED: UNCOATED: SHAPE: DEBOSS: SIDE A: SIDE B: WEIGHT PER UNIT: (uncoated)	<b>CAPSULE</b>  COLOR: BODY: CAP: IMPRINT: BODY: CAP: IMPRINT COLOR: WEIGHT PER UNIT: (net)

TEST	LABEL CLAIM	LIMITS	RESULTS	DATE/DONE BY
IMPURITIES (b) (4)  INDIVIDUAL KNOWN IMPURITIES INDIVIDUAL UNKNOWN IMPURITIES TOTAL (b) (4) (b) (4)	(b) (4)			
ASSAY: METHYLPARABEN*				
ASSAY: PROPYLPARABEN*				
MICROBIAL LIMITS TOTAL PLATE COUNT ESCHERICHIA COLI TOTAL COMBINED MOLDS AND YEASTS COUNT				
DELIVERABLE VOLUME*** (b) (4)				
(b) (4)				

### Stability Specifications

## Chemistry Assessment Section



STABILITY SPECIFICATIONS/SUBMISSION FORM

Page 1 of 2

PRODUCT NAME: HYDROCODONE BITARTRATE AND GUAIFENESIN ORAL SOLUTION		MF #: 1120	
STRENGTH: 2.5 mg/200 mg per 5 mL		(A)NDA #: 22-424	
PRODUCT DESCRIPTION			
LIQUID	TABLET	COATED TABLET	CAPSULE
COLOR: (b) (4) AROMA: Black 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)

LOT NO.: _____	SIZE: _____	INTERVAL: _____	MIKART DEA #PM0142137 #RM0197497, #RM0374203
QUANTITY SUBMITTED: _____	DATE: _____	BY: _____	
SUBMITTED TO: _____		ATTN: _____	

DESIGNATED TESTING FACILITY	TEST PROCEDURE	MINIMUM QUANTITY REQUIRED
MIKART, INC.	FPSPMF1120B	16 FL. OZ.
(b) (4) MIKART	(b) (4)	4 FL. OZ. (b) (4)

### SPECIFICATIONS/RESULTS

TEST	LABEL CLAIM	LIMITS	RESULTS	DATE/DONE BY
APPEARANCE		A transparent liquid with a color that has a black raspberry smell (b) (4)		
pH		(b) (4)		
SPECIFIC GRAVITY				
IDENTIFICATION HYDROCODONE BITARTRATE GUAIFENESIN METHYLPARABEN PROPYLPARABEN				
ASSAY: HYDROCODONE BITARTRATE	2.5 mg per 5 mL			
IMPURITIES (b) (4) INDIVIDUAL KNOWN IMPURITIES INDIVIDUAL UNKNOWN IMPURITIES TOTAL				
ASSAY: GUAIFENESIN	200 mg per 5 mL			
IMPURITIES (b) (4) INDIVIDUAL KNOWN IMPURITIES INDIVIDUAL UNKNOWN IMPURITIES TOTAL (b) (4) (b) (4)				

## Chemistry Assessment Section



STABILITY SPECIFICATIONS/SUBMISSION FORM

Page 2 of 2

<b>PRODUCT NAME:</b> HYDROCODONE BITARTRATE AND GUAIFENESIN ORAL SOLUTION <b>STRENGTH:</b> 2.5 mg/200 mg per 5 mL		<b>MF #:</b> 1120 <b>(A)NDA #:</b> 22-424	
PRODUCT DESCRIPTION			
LIQUID	TABLET	COATED TABLET	CAPSULE
<b>COLOR:</b> (b) (4) <b>AROMA:</b> Black Raspberry	<b>COLOR:</b> <b>SHAPE:</b> <b>DEBOSS:</b> <b>SIDE A:</b> <b>SIDE B:</b> <b>WEIGHT PER UNIT:</b>	<b>COLOR:</b> <b>COATED:</b> <b>UNCOATED:</b> <b>SHAPE:</b> <b>DEBOSS:</b> <b>SIDE A:</b> <b>SIDE B:</b> <b>WEIGHT PER UNIT:</b> (uncoated)	<b>COLOR:</b> <b>BODY:</b> <b>CAP:</b> <b>IMPRINT:</b> <b>BODY:</b> <b>CAP:</b> <b>IMPRINT COLOR:</b> <b>WEIGHT PER UNIT:</b> (net)

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

## Chemistry Assessment Section

**V. EER Summary Report****FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT**

<b>Application:</b>	NDA 22424/000	<b>Sponsor:</b>	TIBER LABS
<b>Org. Code:</b>	570		5400 LAUREL SPRINGS PKY BLDG 800 STE 80:
<b>Priority:</b>	4		SUWANEE, GA 30024
<b>Stamp Date:</b>	29-NOV-2010	<b>Brand Name:</b>	HYDROCODONE BITARTRATE/GUAIFENESIN ORAL
<b>PDUFA Date:</b>	29-SEP-2011	<b>Estab. Name:</b>	
<b>Action Goal:</b>		<b>Generic Name:</b>	HYDROCODONE BITARTRATE/GUAIFENESIN ORAL
<b>District Goal:</b>	31-JUL-2011	<b>Product Number; Dosage Form; Ingredient; Strengths</b>	
			001; SOLUTION; HYDROCODONE BITARTRATE; 2.5MG/5ML 001; SOLUTION; GUAIFENESIN; 200MG/5ML
<b>FDA Contacts:</b>	S. PATWARDHAN	<b>Project Manager</b>	(HF-01) 301-796-4085
	X. SHEN	<b>Review Chemist</b>	301-796-1411
	A. SCHROEDER	<b>Team Leader</b>	301-796-1749

---

<b>Overall Recommendation:</b>	ACCEPTABLE	on 10-AUG-2011	by M. STOCK	(HFD-320)	301-796-4753
	WITHHOLD	on 07-JAN-2011	by F. GODWIN	()	

---

<b>Establishment:</b>	CFN: (b) (4)	FEI: (b) (4)	
		(b) (4)	
<b>DMF No:</b>		<b>AADA:</b>	
<b>Responsibilities:</b>	DRUG SUBSTANCE MANUFACTURER		
<b>Profile:</b>	(b) (4)	<b>OAI Status:</b>	NONE
<b>Last Milestone:</b>	OC RECOMMENDATION		
<b>Milestone Date:</b>	11-JAN-2011		
<b>Decision:</b>	ACCEPTABLE		
<b>Reason:</b>	BASED ON PROFILE		

---

<b>Establishment:</b>	CFN: (b) (4)	FEI: (b) (4)	
		(b) (4)	
<b>DMF No:</b>		<b>AADA:</b>	
<b>Responsibilities:</b>	DRUG SUBSTANCE MANUFACTURER		
<b>Profile:</b>	(b) (4)	<b>OAI Status:</b>	NONE
<b>Last Milestone:</b>	OC RECOMMENDATION		
<b>Milestone Date:</b>	10-JUL-2011		
<b>Decision:</b>	ACCEPTABLE		
<b>Reason:</b>	DISTRICT RECOMMENDATION		

---



# CHEMISTRY REVIEW TEMPLATE



## Chemistry Assessment Section

### FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

**Establishment:** CFN: 1050658 FEI: 1050658  
 MIKART INC  
 1750 CHATTAHOOCHEE AVE NW  
 ATLANTA, GA 303182112

**DMF No:** **AADA:**

**Responsibilities:** FINISHED DOSAGE LABELER  
 FINISHED DOSAGE MANUFACTURER  
 FINISHED DOSAGE PACKAGER  
 FINISHED DOSAGE RELEASE TESTER  
 FINISHED DOSAGE STABILITY TESTER

**Profile:** LIQUIDS (INCLUDES SOLUTIONS, (b) (4) **OAI Status:** NONE  
 (b) (4)

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 10-AUG-2011

**Decision:** ACCEPTABLE

**Reason:** DISTRICT RECOMMENDATION

---

**Establishment:** CFN: (b) (4) FEI: (b) (4)  
 (b) (4)

**DMF No:** **AADA:**

**Responsibilities:** FINISHED DOSAGE OTHER TESTER

**Profile:** CONTROL TESTING LABORATORY **OAI Status:** NONE

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 11-JAN-2011

**Decision:** ACCEPTABLE

**Reason:** BASED ON PROFILE

---

Chemistry Assessment Section

**VI. Nanomaterial Information Table**

<p><b>1) This review contains new information added to the table below:</b> _____ Yes <input checked="" type="checkbox"/> No                  Review date: <u>27-Jul-2011</u></p>
<p><b>2) Are any nanoscale materials included in this application? (If yes, please proceed to the next questions.)</b> Yes _____; No <input checked="" type="checkbox"/>; Maybe (please specify) _____</p>
<p><b>3 a) What nanomaterial is included in the product? (Examples of this are listed as search terms in Attachment B.)</b> _____</p>
<p><b>3 b) What is the source of the nanomaterial?</b></p>
<p><b>4) Is the nanomaterial a reformulation of a previously approved product?</b></p> <p>Yes _____ No _____</p>
<p><b>5) What is the nanomaterial functionality?</b>                  Carrier _____; Excipient _____; Packaging _____                  API _____; Other _____</p>
<p><b>6) Is the nanomaterial soluble (e.g., nanocrystal) or insoluble (e.g., gold nanoparticle) in an aqueous environment?</b>                  Soluble _____; Insoluble _____</p>
<p><b>7) Was particle size or size range of the nanomaterial included in the application?</b>                  Yes _____ (Complete 8); No _____ (go to 9).</p>
<p><b>8) What is the reported particle size?</b>                  Mean particle size _____; Size range distribution _____; Other _____</p>
<p><b>9) Please indicate the reason(s) why the particle size or size range was not provided:</b></p> <p>_____</p> <p>_____</p>
<p><b>10, What other properties of the nanoparticle were reported in the application (See Attachment E)?</b> _____</p>
<p><b>11) List all methods used to characterize the nanomaterial?</b> _____</p>

## Chemistry Assessment Section

**VII. List Of Comments To Be Communicated**

1. Update the revised acceptance limits for impurities and Total Combined Mold/Yeast Count in the stability data summary table in your next stability data update.
2. Please include deficiencies identified by microbiologist Dr. John W. Metcalfe in his 16-Aug-2011 review (filed in DARRTS).

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

/s/  
-----

XIAOBIN SHEN

08/25/2011

This NDA is approvable from CMC perspective pending resolution of microbiology related deficiencies. Please include the comment at the end of the review and the referenced microbiology deficiencies to the applicant in the action letter.

PRASAD PERI

08/26/2011

I concur

**NDA 22-424**

**Proprietary Name is not Provided  
(Hydrocodone Bitartrate and Guaifenesin)  
Oral Solution**

**Tiber Laboratories, LLC**

**Xiaobin Shen, Ph.D.  
for  
Division of Pulmonary, Allergy and Rheumatology Drug  
Products**

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# Chemistry Review Data Sheet

1. NDA 22-424
2. REVIEW #: 1
3. REVIEW DATE: 26-Mar-2011
4. REVIEWER: Xiaobin Shen, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents

NA

Document Date

NA

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original

Amendment 0001

Amendment 0002

Document Date

21-Sept-2010

06-Jan-2011

22-Feb-2011

7. NAME & ADDRESS OF APPLICANT:

Name: Tiber Laboratories, LLC

Address: 5400 Laurel Springs Parkway, Suite 803  
Suwanee, GA 30024

Representative: Cassie Vitolo, Director, Regulatory Affairs

## Chemistry Review Data Sheet

Telephone: (678) 208-0388

Facsimile: (678) 208-0346

## 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Not provided
- b) Non-Proprietary Name (USAN): Hydrocodone Bitartrate and Guaifenesin oral solution
- c) Code Name/# (ONDQA only): N/A
- d) Chem. Type/Submission Priority (ONDQA only):
  - Chem. Type: 4
  - Submission Priority: S

## 9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

The application is filed based on previously approved NDA and existing OTC monographs listed below:

Hydrocodone Bitartrate — Hycomine Syrup, 5 mg/5 mL, NDA 19-410; Hycodan Tablets and Syrup, 5 mg/tablet and 5 mg/5 mL, NDA 05-213.

Guaifenesin — OTC monograph for expectorant drug products, 21 CFR 341.18.

## 10. PHARMACOL. CATEGORY:

Hydrocodone bitartrate is antitussive (cough suppressing); Guaifenesin is an expectorant.

## 11. DOSAGE FORM: Oral Solution

## 12. STRENGTH/POTENCY: 2.5 mg Hydrocodone Bitartrate, and 200 mg Guaifenesin per 5 mL.

## 13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:  Rx  OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

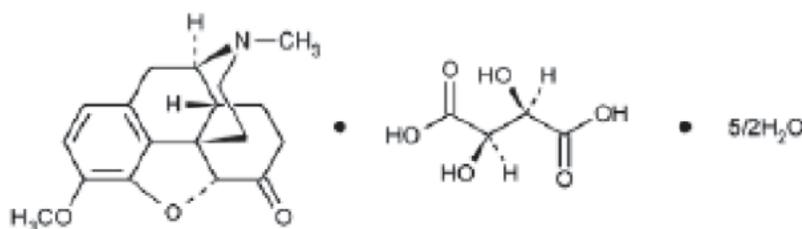
SPOTS product – Form Completed

## Chemistry Review Data Sheet

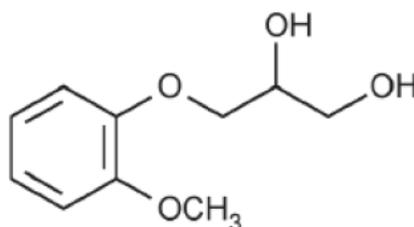
 X  Not a SPOTS product

## 16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

There are two active pharmaceutical ingredients in this product.

Hydrocodone Bitartrate:4,5 $\alpha$ -Epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5)Molecular Formula:  $C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2\frac{1}{2}H_2O$ 

Molecular Weight: 494.490

Guaifenesin: $(\pm)$ -3-(*o*-Methoxyphenoxy)-1,2-propanediolMolecular Formula:  $C_{10}H_{14}O_4$ 

Molecular Weight: 198.22

## 17. RELATED/SUPPORTING DOCUMENTS:

## A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	3	Adequate	06-Oct-2010	NA

Chemistry Review Data Sheet

(b) (4)	(b) (4)				
	II	3	Adequate	20-Dec-2010	NA
	III	4	NA	NA	NA
	III	4	NA	NA	NA
	III	4	NA	NA	NA
	III	4	NA	NA	NA
	III	4	NA	NA	NA
	III	4	NA	NA	NA
	III	4	NA	NA	NA
	III	4	NA	NA	NA

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents:**

Chemistry Review Data Sheet

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NA	NA	NA

18. STATUS:

**ONDQA:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA	NA	NA
EES	Pending		NA
Pharm/Tox	Pending		Dr. Grace Lee
Biopharm	NA	NA	NA
LNC	Pending		
Methods Validation	Validation is not required by FDA Lab	17-Mar-2011	Dr. Xiaobin Shen
EA	Acceptable	17-Mar-2011	Dr. Xiaobin Shen
Microbiology	Acceptable	17-Mar-2011	Dr. James McVey

# The Chemistry Review for NDA 22-424

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls standpoint, the NDA is approvable pending the following:

- Adequate responses to support the outstanding issues summarized at end of this review.
- Adequate EES status upon completion of the manufacturing site inspections.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

No post-marketing items.

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Substance(s) and Drug Product(s)

##### Drug substances

There are two drug substances in this NDA: hydrocodone bitartrate and guaifenesin.

1- Hydrocodone is a semi synthetic narcotic antitussive and analgesic. It exists in fine white crystals or crystalline powder. It is soluble in water and slightly soluble in alcohol. The hydrocodone bitartrate drug substance is manufactured (b) (4) per DMF (b) (4) which was last reviewed in December, 2010 by Dr. Maria R. Manzoni and deemed adequate. Since then no technical amendments have been made to the DMF by 26-Mar-2011. The DMF's facility's EES status is acceptable. The release specifications for hydrocodone bitartrate comply with the USP monograph and ICH Q3A and include appearance, identification, specific rotation, pH, loss on drying, residue on ignition, chloride, (b) (4) impurities, assay, related substances (specified and unspecified), and residual solvents. This drug substance is packaged (b) (4). Its stability data is referenced to DMF (b) (4) which supports the claimed retest period of (b) (4) months.

2- Guaifenesin is an expectorant. It exists as white or off-white crystalline powder. It is odorless or has a slightly characteristic odor. It is soluble in water. The guaifenesin drug substance is manufactured (b) (4) per DMF (b) (4) which was last reviewed in September, 2008 by Dr. Yong-De Lu and deemed adequate. The subsequent amendments were reviewed by Dr. Arthur Shaw last in December, 2010, since then no technical amendments have been made to the DMF by 26-Mar-2011, the DMF remains adequate. The DMF's facility's EES status is

## Chemistry Assessment Section

pending for the Agency's inspection. The release specifications for guaifenesin comply with the USP monograph and ICH Q3A and include appearance, identification, melting range, loss on drying, heavy metal, assay and impurities. This drug substance is packaged (b) (4). Its stability data is referenced to DMF (b) (4) which supports the claimed retest period of (b) (4) months.

**Drug product**

The drug product, hydrocodone bitartrate and guaifenesin oral solution, is a (b) (4) liquid with a black raspberry aroma. It is indicated for (b) (4)

Each 5 mL of the oral solution contains 2.5 mg of hydrocodone bitartrate, and 200 mg of guaifenesin. In addition to the two active pharmaceutical ingredients, it also contains sorbitol, glycerin, saccharin sodium, polyethylene glycol (b) (4) methylparaben, propylparaben, citric acid, sodium citrate, (b) (4) black raspberry flavor, FD&C Blue #1 colorant, D&C Red # 33 colorant, and water as excipients. These excipients are commonly used in oral solution products. The product is packaged into both 4 oz and 16 oz HDPE bottles and closed with child resistant caps.

The drug product is manufactured by Mikart, Inc. at Atlanta, GA. This facility is pending inspection. The drug product release specifications include appearance, pH, specific gravity, identification, assay, (b) (4) impurity, (b) (4) and microbial limits. The stability study was conducted on 3 manufacturing batches for registration. All 3 batches were packaged into the 16 oz HDPE bottles and tested for stability. One of the batch was also packaged into the 4 oz HDPE bottles and tested for stability. Up to 36 months of stability study at real time is planned, up to (b) (4) months of both real time and accelerated stability data are provided. The provided data show no meaningful change in all tested product quality attributes beyond typical analytical variations. Based on ICH Q1E, the provided data support an expiry of (b) (4) months, but not the 24 months claimed by the applicant.

**B. Description of How the Drug Product is Intended to be Used**

The drug product hydrocodone and guaifenesin oral solution is packaged in 4 and 16 fl. oz HDPE bottles. Each 5 mL of the oral solution contains 2.5 mg of hydrocodone bitartrate and 200 mg guaifenesin.

(b) (4)  
The manufacturer proposed a two year expiry with 20 C to 25 C storage condition, the firm provided (b) (4) real time stability data to support the two year expiry and it is found only to support (b) (4) months expiry due to limited data.

## Chemistry Assessment Section

**C. Basis for Approvability or Not-Approval Recommendation**

The NDA submission and amendments provided acceptable information on the chemistry, manufacturing, and controls of the hydrocodone and guaifenesin oral solution. The product is recommended for approval, pending resolution of the outstanding issues summarized at end of this review and acceptable EES status for the guaifenesin and drug product manufacturers, based on the following:

- The drug substance and product specifications provide adequate controls;
- The drug product excipients are of USP/NF grade or have been evaluated and deemed acceptable;
- The drug product container closure systems are acceptable for pharmaceutical use;
- Both drug substance and drug product are stable in the studied stability period and support <sup>(b)</sup><sub>(4)</sub> months of drug product expiry.

**III. Administrative****A. Reviewer's Signature**

Chemist: Xiaobin Shen, Ph.D. {Signed electronically in DARRTS}

**B. Endorsement Block**

ChemistName/Date:

ChemistryTeamLeaderName/Date:

ProjectManagerName/Date:

**C. CC Block**

## Chemistry Assessment Section

Chemistry Assessment**I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2:  
Body Of Data**

There are two drug substances in the drug product, namely, hydrocodone bitartrate (b) (4) and guaifenesin (b) (4). The review of this section is organized by drug substance.

**S DRUG SUBSTANCE – Hydrocodone Bitartrate (b) (4)****S.1 General Information****S.1.1 Nomenclature**

INN: Hydrocodone bitartrate

**Compendial Name:** Hydrocodone bitartrate

**Chemical Names:** Morphinan-6-one, 4,5-epoxy-3-methoxy-17-methyl-, (5 $\alpha$ )-, [R-(R\*,R\*)]-2,3-dihydroxybutanedioate (1:1), hydrate (2:5)

and

4,5 $\alpha$ -Epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1)  
hydrate (2:5)

**Chemical Abstracts Services (CAS) Registry Number:** 34195-34-1

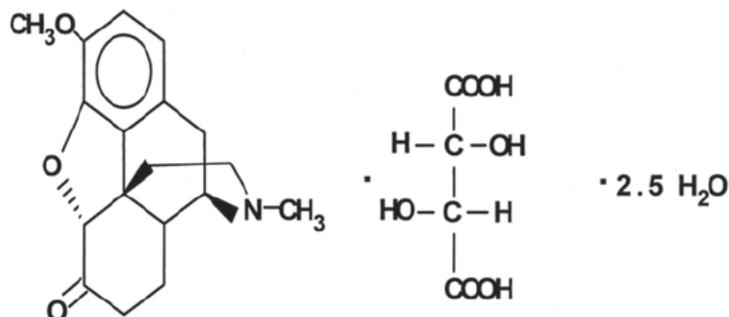
**Evaluation:** Adequate.

**S.1.2 Structure**

Molecular Formula: C<sub>18</sub>H<sub>21</sub>NO<sub>3</sub> · C<sub>4</sub>H<sub>6</sub>O<sub>6</sub> · 2.5 H<sub>2</sub>O

Molecular Weight: 494.490

Structural Formula:



**Evaluation:** Adequate.

**S 1.3 General Properties**

## Chemistry Assessment Section

**Hydrocodone bitartrate** is a fine white crystal or a crystalline powder. It is soluble in water (b) (4) slightly soluble in alcohol (b) (4) and almost insoluble in ether and chloroform. The pH of (b) (4) % aqueous solution is approximately (b) (4). The specific rotation is between (b) (4)°.

**Evaluation:** Adequate.

**S.2 Manufacture [Hydrocodone Bitartrate**

(b) (4)

(b) (4)

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## Chemistry Assessment Section

**Evaluation:** Acceptable. The specifications meet all USP requirements for hydrocodone. The impurity specifications meet ICH Q3A.

**S.5 Reference Standards or Materials [Hydrocodone Bitartrate,**

(b) (4)]  
USP hydrocodone bitartrate reference standards were used. The drug product manufacturer used USP hydrocodone bitartrate reference standard lot M0G061 on testing of drug substance lot 10R0014.

**Evaluation:** Adequate.

**S.6 Container Closure System [Hydrocodone Bitartrate (b) (4)**

] The hydrocodone bitartrate drug substance is packaged (b) (4). DMF (b) (4) was referenced for further information.

**Evaluation:** Adequate.

**S.7 Stability [Hydrocodone Bitartrate (b) (4)]****S.7.1 Stability Summary and Conclusions**

(b) (4) month retest date is used based on DMF holder assignment of a (b) (4) retest period. DMF (b) (4) was referenced for further information.

**Evaluation:** Adequate.

**S.7.2 Postapproval Stability Protocol and Stability Commitment****S.7.3 Stability Data**

Both S.7.2 and S.7.3 were referenced to DMF (b) (4)

**Evaluation:** Adequate.

## Chemistry Assessment Section

S DRUG SUBSTANCE – Guaifenesin, (b) (4)

S.1 General Information

S.1.1 Nomenclature

INN: Guaifenesin

Compendial Name: Guaifenesin

Chemical Names: 1,2-Propanediol, 3-(2-methoxyphenoxy)-(+/-)-

Chemical Abstracts Services (CAS) Registry Number: 93-14-1

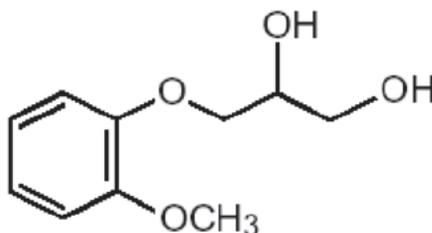
Evaluation: Adequate.

S.1.2 Structure

Molecular Formula: C<sub>10</sub>H<sub>14</sub>O<sub>4</sub>

Molecular Weight: 198.22

Structural Formula:



Evaluation: Adequate.

S 1.3 General Properties

Guaifenesin is a white or off-white crystalline powder. It is odorless or has a slightly characteristic odor. It is soluble in water. It melts between 78° and 82°C.

Evaluation: Adequate.

S.2 Manufacture [Guaifenesin, (b) (4)]

(b) (4)

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## Chemistry Assessment Section

**S.4.5** *Justification of Specification*

The specification complies with the USP monograph for guaifenesin.

**Evaluation:** Acceptable. This is acceptable in consideration of the usage history of guaifenesin. However, as noted in section S.4.4, the specifications can be tightened based on actual data in consideration of ICH Q3A. Pharmacology/toxicology reviewer Dr. Grace Lee has been consulted to evaluate acceptability of the specification.

**S.5** **Reference Standards or Materials [Guaifenesin (b) (4)**

(b) (4)  
USP guaifenesin reference standards (Lot I1C098 and J0G257) were used.

**Evaluation:** Adequate.

**S.6** **Container Closure System [Guaifenesin (b) (4)]**

The guaifenesin drug substance is packaged (b) (4)  
(b) (4) It referenced to DMF (b) (4) for further information.

**Evaluation:** Adequate.

**S.7** **Stability [Guaifenesin (b) (4)]****S.7.1** *Stability Summary and Conclusions*

(b) (4) retest date is set based on long term stability data, it referenced to DMF (b) (4) for further stability information.

**Evaluation:** Adequate.

**S.7.2** *Postapproval Stability Protocol and Stability Commitment***S.7.3** *Stability Data*

Both S.7.2 and S.7.3 referenced to DMF (b) (4)

**Evaluation:** Adequate.

Chemistry Assessment Section

**P DRUG PRODUCT [Hydrocodone and Guaifenesin, Oral Solution]**

**P.1 Description and Composition of the Drug Product [Hydrocodone and Guaifenesin, Oral Solution]**

Hydrocodone and guaifenesin oral solution is a (b) (4) liquid with a black-raspberry aroma. Each 5 milliliter of the solution contains 2.5 mg of hydrocodone bitartrate and 200 mg of guaifenesin as the active ingredients.

The drug product quantitative composition is reproduced below –

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		
Polethylene Glycol (b) (4) NF		NF		
(b) (4) Black Raspberry Flavor		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

In Section 3.2.P.4.1. Specifications (b) (4) is provided (reproduced below).

## Chemistry Assessment Section

(b) (4)



The product is packaged into both 4 oz HDPE and 16 oz HDPE bottle configurations. The packaging information provided is reproduced below —

4 oz Packaging Size Lot # B100058B

(b) (4)



16 oz Packaging Size Lot # B100056A, B100057A, B100058A

(b) (4)



## Chemistry Assessment Section

**Evaluation:** Acceptable. (b) (4) all ingredients are of compendial grade and used within limits of already approved oral solution products.

The (b) (4) black raspberry flavor is not listed in the Inactive Ingredient database of approved drug products. However, based on the drug product formulation composition, the maximum dose of the flavor administered each day (b) (4) is then calculated to be (b) (4) mg. Pharmacology/toxicology reviewer Dr. Grace Lee has been consulted on 09-Mar-2011 for the evaluation of its safety.

## P.2 Pharmaceutical Development [Hydrocodone and Guaifenesin, Oral Solution]

### P.2.1 Components of the Drug Product

#### P.2.1.1 Drug Substance

No drug substance related development information is provided. Instead, the applicant referenced to a drug product manufacturing process transfer report.

**Evaluation:** Acceptable. The product is a marketed unapproved oral solution. The established drug product manufacture process and stability data indicate that it does not necessitate additional development effort for the purpose of this NDA review. This is also applicable for all the following pharmaceutical development related sections.

#### P.2.1.2 Excipients

The applicant provided a list of the excipients and their corresponding formulation functions, but not excipient related development information.

**Evaluation:** Acceptable.

### P.2.2 Drug Product

#### P.2.2.1 Formulation Development

The applicant provided no formulation development information.

**Evaluation:** Acceptable.

#### P.2.2.2 Overages

No overages are included in the formulation.

**Evaluation:** Adequate.

#### P.2.2.3 Physicochemical and Biological Properties

The applicant provided no related information.

1) This review contains new information added to the table below: \_\_\_\_\_ Yes  No  
Review date: \_20-Mar-2011\_

## Chemistry Assessment Section

2) Are any nanoscale materials included in this application? (If yes, please proceed to the next questions.) Yes _____; No <u>X</u> ; Maybe (please specify) _____
3 a) What nanomaterial is included in the product? (Examples of this are listed as search terms in Attachment B.) _____
3 b) What is the source of the nanomaterial?
4) Is the nanomaterial a reformulation of a previously approved product? Yes _____ No _____
5) What is the nanomaterial functionality? Carrier _____; Excipient _____; Packaging _____ API _____; Other _____
6) Is the nanomaterial soluble (e.g., nanocrystal) or insoluble (e.g., gold nanoparticle) in an aqueous environment? Soluble _____; Insoluble _____
7) Was particle size or size range of the nanomaterial included in the application? Yes _____ (Complete 8); No _____ (go to 9).
8) What is the reported particle size? Mean particle size _____; Size range distribution _____; Other _____
9) Please indicate the reason(s) why the particle size or size range was not provided: _____ _____
10, What other properties of the nanoparticle were reported in the application (See Attachment E)? _____
11) List all methods used to characterize the nanomaterial? _____

**Evaluation:** Acceptable.

**P.2.3 Manufacturing Process Development**

The applicant provided no related information.

**Evaluation:** Acceptable.

**P.2.4 Container Closure System**

The NDA stated that the container closure systems that are used with Hydrocodone Bitartrate and Guaifenesin Oral Solution, 2.5 mg/200 mg per 5 mL are \_\_\_\_\_

(b) (4)

## Chemistry Assessment Section

(b) (4) USP testing was performed for each proposed container/closure system upon initial receipt by Mikart.

**Evaluation:** Acceptable. Apparently there is no development information submitted, the container closure system suitability will be evaluated in Sections 3.2.P.7 and 3.2.P.8.

**P.2.5                    Microbiological Attributes**

Microbial analysis is performed according to specifications for the finished product during release and stability testing. Additionally, Purified Water USP raw material is subjected to microbial testing prior to release.

**Evaluation:** Acceptable.

**P.2.6                    Compatibility**

Not applicable. There are no reconstituting diluents or dosage devices for this product.

**Evaluation:** Adequate.

**P.3                    Manufacture [Hydrocodone and Guaifenesin, Oral Solution]**

(b) (4)

19 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

Chemistry Assessment Section

**Evaluation:** Acceptable. The USP testing results of the container closures are noted as dated 2000.

**P.8 Stability [Hydrocodone and Guaifenesin, Oral Solution]**

**P.8.1 Stability Summary and Conclusion**

**Stability test specifications**

The stability samples are tested against the following stability specifications.

Tests	Specification	Analytical Procedure
APPEARANCE	A transparent liquid with a (b) (4) color that has a black raspberry smell.	Visual
pH	(b) (4)	FPSPG001
SPECIFIC GRAVITY	(b) (4)	FPSPG002
IDENTIFICATION		
Hydrocodone Bitartrate	RT's compare to standard	FPSPMF1120B
Guaifenesin	RT's compare to standard	FPSPMF1120B
Methylparaben	RT's compare to standard	FPSPMF1120B
Propylparaben	RT's compare to standard	FPSPMF1120B
ASSAY AND IMPURITIES		
Hydrocodone Bitartrate	(b) (4) %	FPSPMF1120B
(b) (4)	NMT (b) (4) %	FPSPMF1120B
Any other Individual	NMT %	FPSPMF1120B
Total	NMT %	FPSPMF1120B
Guaifenesin	(b) (4) %	FPSPMF1120B
(b) (4)	NMT (b) (4) %	FPSPMF1120B
(b) (4)	NMT %	FPSPMF1120B
Any Other Individual	NMT %	FPSPMF1120B
Total (b) (4)	(b) (4) NMT %	FPSPMF1120B
(b) (4)	(b) (4) %	FPSPMF1120B
Methylparaben	(b) (4) %	FPSPMF1120B
Propylparaben	%	FPSPMF1120B
MICROBIAL LIMITS*		
Total Plate Count	NMT (b) (4) CFU	USP <61>
Total Combined Molds and Yeasts Count	NMT CFU	USP <61>
E. Coli	Absent	USP <62>
(b) (4)		

The analytical method, referenced as FPSPMF1120B, is the same as that used in release and evaluated in section 3.2.P.5.2. The specifications are also the same as that for release testing.

**Stability test protocols**

The stability test protocols for both the 4 oz and 16 oz configurations are the same. The related information are reproduced below.

Chemistry Assessment Section



(b) (4)

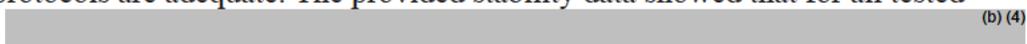
**Stability test conclusions**

The applicant concluded that  (b) (4)

The applicant proposed the following expiration for the drug product. The rationale of the proposal is  (b) (4)

PACKAGING SIZE	PROPOSED EXPIRATION DATE	SUPPORTING DATA
4 oz container	2 years	 (b) (4)
16 oz container	2 years	

**Evaluation:** Inadequate. The specifications have the same deficiencies as outlined for the release testing specifications. The applicant will be requested to amend both specifications.

The test protocols are adequate. The provided stability data showed that for all tested attributes  (b) (4)

## Chemistry Assessment Section

(b) (4)

The 4 oz product package configuration has the same formulation as that packaged as the 16 oz product. There is only 1 exhibit lot of the 4 oz package configuration in both release and stability testing. The Agency considers this acceptable as the package size is not likely to cause any stability difference based on rationales listed below:

(b) (4)

Per ICH Q1E, up to (b) (4) months of expiry can be assigned.

**Deficiency:** The provided stability testing specifications have the same deficiencies as outlined for the release testing specifications. The provided stability data only support (b) (4) months expiry.

**P.8.2 Postapproval Stability Protocol and Stability Commitment**

The applicant stated that they will assure that the necessary studies are conducted (b) (4)

Stability results will be submitted at the time intervals, and in the format specified by the FDA (b) (4)

The applicant will withdraw from the market any batches found to be out of approved specifications for the drug product.

**Evaluation:** Adequate.

**P.8.3 Stability Data**

Individual stability data is provided for all 4 lots (3 lots for the 16 oz package configuration, 1 lot for the 4 oz package configuration) tested at all stipulated conditions (b) (4) See evaluation of result summary in Section P.8.1. Overall the stability data indicate that the product is stable at all tested conditions. All tested attributes had (b) (4)

**Evaluation:** Inadequate. The provided stability data is insufficient to support the 2 years of expiration claimed.

**Deficiency:** Provide at least 12 month real time stability data to support the proposed two year shelf life.

**A APPENDICES**

**A.1 Facilities and Equipment (biotech only)**

## Chemistry Assessment Section

Not applicable.

**A.2 Adventitious Agents Safety Evaluation**

Not applicable.

**A.3 Novel Excipients**

There are no novel excipients used.

**R REGIONAL INFORMATION****R1 Executed Batch Records**

A copy of the executed batch record for all registration batches are provided.

**Evaluation:** Adequate.

**R2 Comparability Protocols**

There is no proposed comparability protocol (b) (4)

**R3 Methods Validation Package**

Representative samples and all documents are immediately available upon request.

**Evaluation:** Adequate.

**II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1****A. Labeling**

Hydrocodone and guaifenesin oral solution is packaged into both 4 oz and 16 oz HDPE bottles.

The 4 oz product bottle label image is reproduced below.



## Chemistry Assessment Section

The 16 oz product bottle label image is reproduced below.



**Evaluation:** Acceptable.

**B. Package Insert**

The package insert is provided, a parallel comparison to that of the RLD Hycodan is also provided.

**Evaluation:** Acceptable. The following changes are recommended.

- In the Description section, list the components of the oral solution in alphabetical order.

**C. Environmental Assessment Or Claim Of Categorical Exclusion**

The applicant requested a categorical exclusion; the basis is that the proposed action does not increase the use of the active moiety per 21 CFR 25.31(a) and there are no extraordinary circumstances that may significantly affect the quality of the human environment per 21 CFR 25.21.

**Evaluation:** Adequate.

## Chemistry Assessment Section

**III. List of Deficiencies to be Communicated**

1. The guaifenesin drug substance impurity limits that you transcribed from guaifenesin USP monograph do not incorporate (b) (4) this is misleading. Amend your impurity analysis method to include (b) (4) in the impurity result calculation. Also update the guaifenesin drug substance specification table with the corrected drug substance impurity specifications, which are also modified in consideration of ICH Q3A.
2. The guaifenesin drug substance specifications for other individual impurities do not meet ICH Q3A requirements. Tighten the specifications in consideration of both ICH Q3A and test results.
3. Drug product manufacturing process related comments are listed below.
  - A. (b) (4)
  - B. (b) (4)  
Clarify this hold duration time limit in the manufacturing process section and master batch record.
  - C. Provide product stability and microbial limit data to support your maximum product solution hold duration.
4. Provide the (b) (4) release testing requirements for all excipients. At least an identification test is required if the excipient is accepted on the basis of a Certificate of Analysis and is used within its retest period.
5. Drug product release and stability specifications related comments are listed below.
  - A. The specifications table has acceptance criteria for pseudoephedrine, which is not a component of this product. Update the specification table to remove the entry.
  - B. There is only one identification test for each drug substance. Include a complementary identification test.
  - C. Add a deliverable volume test to the product at 4 oz package configuration. USP <698> requires this test when the product is labeled to contain not more than 250 mL.
  - D. The drug product impurity acceptance criteria should follow ICH Q3B. At the proposed total daily dose for both hydrocodone and guaifenesin, impurities not less than (b) (4)% should be identified, impurities not less than (b) (4)% should be qualified. The acceptance criteria of NMT (b) (4)% for any other individual impurity is not acceptable if there are unidentified impurities in this category. We recommend you to segregate the identified and unidentified impurities and establish the corresponding acceptance criteria in reference to ICH Q3B. Impurities in the drug product not less than (b) (4)% should be qualified.
  - E. The total combined molds and yeasts count acceptance criterion of NMT (b) (4) CFU for the drug product is (b) (4) the USP <1111> recommended limit of NMT 20 cfu/g or mL for aqueous oral solution. Tighten the limit.

## Chemistry Assessment Section

- F. Conduct forced degradation studies of the drug product to identify potential degradants in reference to the known drug substance related impurities and degradants.
6. Clarify if the original method used by Propharma to analyze hydrocodone and guaifenesin in the drug product was ever validated. Provide the original method validation report, or validate it per ICH Q2 (R1).
  7. Provide a validation report for the method used to analyze methylparaben and propylparaben in the drug product. The validation should be conducted per ICH Q2 (R1).
  8. Provide representative chromatograms for related substance analysis for hydrocodone and guaifenesin in the drug product with appropriate zoom level to show adequate peak separation and proper integration. Address the following comments. The hydrocodone related substance chromatograms provided along with the batch analysis results are too crowded to identify individual peaks (b) (4).  
The guaifenesin related substance chromatogram has a unknown and placebo peak crowded together (b) (4).  
It is not clear if the peaks are adequately separated.
  9. Provide example chromatograms for the analysis of (b) (4) (methylparaben and propylparaben) in the drug product.
  10. The provided stability data only support (b) (4) months expiry per ICH Q1E. Provide at least 12 month real time stability data to support the proposed two year shelf life.
  11. In the Description section of the package insert, list the components of the oral solution in alphabetical order.
  12. USP (b) (4) requires that (b) (4) on the product label; update the label accordingly.
  13. Provide test method(s) for detection and quantification of container closure leachables (b) (4) along with appropriate validation information.
  14. Clarify if the drug product manufacturing process is the same or equivalent to that used to manufacture the drug product for the clinical studies. Otherwise clarify the differences.
  15. The CAS registry number provided for hydrocodone bitartrate drug substance is for the anhydrous form. The CAS registry number for the hydrated form is 34195-34-1. Correct the CAS registry number.

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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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XIAOBIN SHEN

04/26/2011

This NDA is approvable pending resolution of deficiencies listed at end of review. An information request will be communicated to the applicant.

PRASAD PERI

04/27/2011

I concur

**OND Division of Pulmonary Allergy and Rheumatology Products**  
**Initial Quality Assessment**  
**Date: January 7, 2011**

**NDA: 22-424**

**Applicant:** Tiber Laboratories, LLC (Suwanee, GA)

**Stamp Date:** November 29, 2010

**PDUFA Date:** September 29, 2011

**ONDQA 5 month date:** April 30, 2011

**Type of New Drug Application:** 505(b)(2), reference listed drug is Hycodan Tablets and Syrup (Endo): NDA 5-213

**Proposed Proprietary Name:** none

**Established Name:** Hydrocodone and guaifenesin oral solution

**Dosage form and strength:** solution, hydrocodone bitartrate 2.5 mg and guaifenesin 200 mg per 5 mL

**Route of Administration:** oral

**Indications:** [REDACTED] (b) (4)

**CMC Lead (acting):** Alan C. Schroeder, Ph.D. /DNDQA III/ONDQA

**Filability recommendation:** Fileable

**Review team recommendation:** Single primary reviewer (Dr. Xiaobin Shen)

**Time goals:**

- Initial Quality Assessment in DFS: January 28, 2011
- Filing decision “Day 45”: January 13, 2011
- Filing review issues “Day 74”: February 11, 2011
- **Chemistry Review (DR/IR) letter: by April 29, 2010**
- Mid-cycle meeting “Month 5”: April 26, 2010
- Wrap Up meeting: August 2, 2010
- **Final Chemistry Review “Month 8” in DFS: July 29, 2011**
- PDUFA: September 29, 2011

CONSULTS/ CMC RELATED REVIEWS	COMMENT
Biopharm	Not necessary
CDRH	Not necessary
EA	To be assessed by Primary Reviewer
EES	EER – currently in draft form
DMETS	Labeling consult request will be sent as part of DPARP’s request.
Methods Validation	Methods validation for non-compendial methods may be requested of FDA laboratories if deemed necessary by the reviewer after test methods are finalized.
Microbiology	A consult may be considered for the microbial limits test method [REDACTED] (b) (4) [REDACTED] The test methods need to be requested.

CONSULTS/ CMC RELATED REVIEWS	COMMENT
Pharm/Tox	Potential DS and DP impurities/degradants/leachables to be evaluated for safety.

## Review Notes:

### Drug substance

#### Hydrocodone bitartrate USP

Compendia Name: Hydrocodone Bitartrate

Chemical Name(s): Morphinan-6-one, 4,5-alpha-epoxy-3-methoxy-17-methyl-, (5a)-, [R(R\*,R\*)]-2,3-dihydroxybutanedioate (1:1), hydrate, (2:5)

4,5 $\alpha$ -epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5)

Mikart Code: 0127

CAS registry number: 143-71-5

CMC information for hydrocodone bitartrate is referenced to (b) (4) DMF (b) (4). This DMF was found adequate for a solid oral dosage form, in a review by Maria Manzoni (entered into DARRTS on 12/21/2010). In addition, an information request was sent to the DMF Holder on 12/23/2010.

Confirmation of the hydrocodone bitartrate structure is by comparison of (b) (4) hydrocodone bitartrate with the USP RS (UV and IR data are compared).

The NDA contains specifications for hydrocodone bitartrate (see below). All of the tests are referenced to the USP monograph for hydrocodone bitartrate, except for the methods for residual solvents (GC) and related substances. The applicant indicates that they have transferred the methods for residual solvents and related substances from the vendor. They have conducted methods transfer testing (but not full validation testing) of these non-USP (b) (4) methods since they say the (b) (4) methods are validated. Tests conducted after the (b) (4) retesting period are listed in the NDA. The applicant has also provided some method verification testing for the (b) (4) (impurity) method; this method uses the European Pharmacopeial method for related substances (b) (4).

The following specifications are from the Quality Overall Summary.

<b>Hydrocodone Bitartrate USP</b>		
<b>Manufacturer:</b> (b) (4)		
<b>DMF No.:</b> (b) (4)		
Test	Method	Limits
Appearance	Fine, white crystals or a crystalline powder	Meets Description
Identification Test A	(b) (4)	Compares to in house standard
Identification Test B		Compares to in house standard
Specific Rotation		(b) (4)
pH		(b) (4)
Loss on Drying	USP	(b) (4)
Residue on Ignition	(b) (4)	
Residual Solvents	(b) (4)	
Chloride	USP	
Assay	USP	

(b) (4)

The following specifications include data accepted on the basis of a COA (from 3.2.S.4.1.1



RAW MATERIAL SPECIFICATIONS, RECEIPT AND ANALYSIS

(b) (4)  
(b) (4)

(b) (4)

Acceptance criteria within the Hydrocodone Bitartrate specifications include those of the USP monograph for hydrocodone bitartrate, plus the additional specification for appearance. Note that related substances are apparently reported on the supplier's COA and the results are apparently revalidated (b) (4) specifications for Hydrocodone Bitartrate also include additional tests. *Note that (b) (4) is a potential impurity with a structural alert and the maximum level permitted by the proposed specifications should be evaluated by the pharm/tox reviewer. Methods other than those in the USP monograph will have to be evaluated for suitability by the reviewer. The reviewer should also evaluate differences in the specifications between the supporting DMF (b) (4) and the NDA, and should determine whether any additional testing performed by the DMF holder should be routinely performed by the NDA applicant. In any case, the reviewer should make sure that there is periodic independent verification (by the applicant or an independent third party laboratory) of any results for the drug substance accepted on the basis of a COA, and that the applicant has provided the non-compendial analytical methods to be used (along with appropriate validation data). In addition, the applicant should specify where this testing will be performed. All of this also applies to the excipients used to manufacture the drug product.*

Batch analyses data are provided, and justification of specifications are very briefly provided (i.e. it is stated that the specifications match those of USP and of the vendor). A USP hydrocodone bitartrate reference standard was used. The container closure is very briefly described and reference is made to information in DMF (b) (4)

The summary of stability data, the post-approval stability protocol, and the stability data are cross-referenced to DMF (b) (4)

**Guaifenesin USP**

Compendia Name: Guaifenesin

Chemical Name(s): 1,2-Propanediol, 3-(2-methoxyphenoxy)-(+/-)-

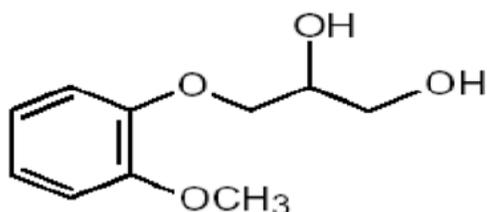
Mikart Code: 1030

CAS registry number: 93-14-1

Molecular Formula: C<sub>10</sub>H<sub>14</sub>O<sub>4</sub>

Molecular Weight: 198.22

Structural Formula:



CMC information is referenced to DMF (b) (4). This DMF was previously reviewed and signed into DARRTS on 10/03/2008. It was found to be adequate (b) (4). Subsequent to this review, additional quality information was submitted to the DMF which needs to be reviewed.

Impurities (and their structural formulae) are described in Section 3.2.S.3. Confirmation of the structure of the drug substance is provided by comparing the (b) (4) drug substance with USP Guaifenesin reference standard (by UV and IR methods). (b) (4)

The NDA contains NDA specifications for Guaifenesin as well as those of the DMF. The NDA test procedures are referenced to the USP monograph for Guaifenesin, except for the tests for assay and chromatographic purity. The test for chromatographic purity is a modified USP method and the test is described. (b) (4)

The vendor's methods for assay and chromatographic purity are said to be used and information about their transfer is in section 3.2.R.3.S.4. *Methods other than those in the USP monograph will have to be evaluated for suitability by the reviewer. The reviewer should also evaluate differences in the specifications between the supporting DMF (b) (4) and the NDA, and should determine whether any additional testing performed by the DMF holder should be routinely performed by the NDA applicant. In any case, the reviewer should make sure that there is periodic independent verification (by the*

*applicant or an independent third party laboratory) of any results for the drug substance accepted on the basis of a COA, and that the applicant has provided the non-compendial analytical methods to be used (along with appropriate validation data). In addition, the applicant should specify where this testing will be performed. All of this also applies to the excipients used to manufacture the drug product.*

Batch analyses data are provided, and justification of specifications are very briefly provided (i.e. it is stated that the specifications match those of USP and of the vendor). A USP guaifenesin reference standard was used. The container closure is very briefly described and reference is made to information in DMF (b) (4)

The summary of stability data, the post-approval stability protocol, and the stability data are cross-referenced to DMF (b) (4)

<b>Guaifenesin USP</b>		
<b>Manufacturer:</b> (b) (4)		
<b>DMF No.:</b> (b) (4)		
Test	Method	Limits
Appearance	White to slightly gray, crystalline powder; may have a slight characteristic odor	Meets description
Identification Test A	(b) (4)	Compares to in house standard
Identification Test B		Compares to in house standard
Identification Test C		(b) (4)
Melting Range		
Loss on Drying		
Heavy Metals		
Chromatographic Purity	Current USP	
(b) (4)		
- any other individual impurity		
- total impurities	(b) (4)	(u) (4)
Assay	Current USP	(b) (4)

**Drug product**

This drug product was originally developed by Propharma, Inc., and the formula and the process were subsequently transferred to Mikart.

Manufacturing sites:

<b>Manufacturing Site</b>
Mikart, Inc. 2090 Marietta Blvd. Atlanta, GA 30318  CFN# 1050658 Ready for Inspection
<b>Packaging/Labeling Site</b>
Mikart, Inc. 1750 Chattahoochee Ave. Atlanta, GA 30318  CFN# 1050658 Ready for Inspection
<b>Testing Site (Raw Material, In-Process, Finished Product, and Stability)</b>
Mikart, Inc. 1595 Chattahoochee Ave. Atlanta, GA 30318  CFN# 1050658 Ready for Inspection



Composition:

% w/v	mg/5mL	Ingredient	Function	g per Liter
0.050	2.5	Hydrocodone Bitartrate USP	Active Ingredient	0.500
4.000	200.0	Guaifenesin USP	Active Ingredient	40.00
(b) (4)		Sorbitol (b) (4) USP	(b) (4)	(b) (4)
		Glycerin USP		
		Polyethylene Glycol (b) (4) NF		
		Methylparaben NF		
		Propylparaben NF		
		Citric Acid (b) (4) USP		
		Sodium Citrate (b) (4) USP		
		Saccharin Sodium		
		D & C Red #33		
		FD & C Blue #1		
		(b) (4) Black Raspberry Flavor (b) (4)		
		Purified Water USP		

The applicant claims that the excipients are all within the limits of the Inactive Ingredient Guide for approved marketed drug products in the US. (This may not apply to the colors and the flavor.) The reviewer should verify that this is true, for oral dosage forms.

Drug Product Specifications:

Test	Specification	Method
Appearance	A transparent liquid with a (b) (4) color that has a black raspberry smell	Visual
pH	(b) (4)	FPSPG001
SPECIFIC GRAVITY		FPSPG002
IDENTIFICATION: Hydrocodone Bitartrate Guaifenesin Methylparaben Propylparaben	RT's compare to standard	FPSPMF1120A (Attachment <b>3.2.P.5.1.1</b> )
ASSAY: HYDROCODONE BITARTRATE (b) (4)	(b) (4) %	
IMPURITIES (b) (4)	NMT (b) (4) %	
Any other Individual	NMT (b) (4) %	
Total	NMT (b) (4) %	
ASSAY: GUAIFENESIN (b) (4)	(b) (4) %	
IMPURITIES (b) (4)	NMT (b) (4) %	
Any other Individual	NMT (b) (4) %	
Total (b) (4)	NMT (b) (4) %	
(b) (4)		
ASSAY: PSEUDOEPHEDRINE HYDROCHLORIDE (b) (4)	(b) (4) %	
IMPURITIES: Any other Individual	NMT (b) (4) %	
Total	NMT (b) (4) %	
ASSAY: METHYLPARABEN* (b) (4)	(b) (4) %	
ASSAY: PROPYLPARABEN* (b) (4)	(b) (4) %	
MICROBIAL LIMITS:		

Test	Specification	Method
Total plate count	NMT (b) (4) CFU	USP <61>
Escherichia coli	Absent	USP <62>
Total combined molds and yeasts count	NMT (b) (4) CFU	
(b) (4)	(b) (4)	N/A
ADDITIONAL TESTING NOT REQUIRED FOR RELEASE		
(b) (4)		

Container Closure System:

- 16 oz. container (b) (4)

- 4 oz. container [REDACTED] (b) (4)

Drug Product Stability:

- [REDACTED] (b) (4) data in both container closure systems are provided for both accelerated (40 deg./75%RH) and long-term (25 deg./60%RH) stability conditions. [REDACTED] (b) (4)
- Stability data are said to be within the proposed specifications.
- Proposed expiry is 24 months.

Batch size for “exhibit batches” (submission batches # B100056A, B100057A and B100058A&B) in the NDA is [REDACTED] (b) (4) and the proposed commercial batch size will be [REDACTED] (b) (4). The proposed scale up will use equipment claimed to be of the same operating principle.

The reviewer should assess whether storage of the drug product in different orientations has any affect on stability for the NDA stability batches. This may influence review of the post-approval stability protocol.

Post Approval Stability Protocol:

See next page.

**What is the post approval stability protocol?**

Number of batches per strength per year and batch sizes	(b) (4)
Tests and acceptance criteria	
Container closure system(s)	
Testing frequency	
Storage conditions (and tolerances) of samples	
Other	
Expiry Date	
Deviations	

Note: The reviewer needs to assess appropriateness of post-approval stability batches not being studied under accelerated conditions, based on the NDA stability data.

Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED
(b) (4)	II		(b) (4)
	II		
	III		

Supporting Device Master File (MAF):

Letters of authorization for the above DMFs: yes, in section 1.4.

IND and history for this drug product:

This product is related to the product which is a three drug combination, including hydrocodone bitartrate, guaifenesin and pseudoephedrine hydrochloride (as an oral solution); this three drug product was purchased from Propharma. There was a Pre-IND meeting with Propharma in March 2007 for IND 76,365 followed by IND 76,365. Propharma filed the application under NDA 22-279 on October 21, 2008. Tiber Labs purchased the NDA on March 25, 2009. This application has not yet been approved.

Tiber has now submitted N22-424 as a new NDA for the two drug combination: hydrocodone bitartrate and guaifenesin (oral solution)

Filing Check List (reproduced from filing meeting slides):

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	x		
2	Is the section indexed and paginated adequately?	x		
3	On its face, is the section legible?	x		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	x		
5	Is a statement provided that all facilities are ready for GMP inspection?	x		This information is with the list of manufacturing sites, as well as in the amendment dated 1/06/2011.
6	Has an environmental assessment report or	x		

	category exclusion been provided?			
7	Does the section contain controls for the drug substance?	x		
8	Does the section contain controls for the drug product?	x		
9	Have stability data and analysis been provided to support the requested expiration date?		x	Stability data have been provided but they are for (b) (4) months and they do not support the requested expiration dating period. No analysis has been provided of the data but the data are not extensive.
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?			Unknown – IND number has not been found yet.
11	Have draft container labels been provided?	x		Only the text of the immediate container and carton labels is provided. The applicant needs to provide color mockups of each actual label.
12	Has the draft package insert been provided?	x		
13	Has an investigational formulations section been provided?		x	The applicant has not suggested that there were different investigational formulations.
14	Is there a Methods Validation package?		x	There is no methods validation package and there seems to be no methods validation reports for drug substance or drug product methods. For the drug substances it appears that the applicant has provided method transfer and method verification reports for non-compendial methods transferred from the drug substance manufacturers to the drug product manufacturer (Mikart). There is a transfer report for the drug product method for assay and related substances for the drug product, but no validation report for this method. There are no validation reports for other drug product methods (b) (4)

				microbial limits).
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Certain review issues which were noted are listed below for consideration by the reviewer

Methods validation – see the filing check list above. The applicant should provide methods validation data for relevant non-compendial methods (e.g., chromatographic methods, microbiological assays) as per the ICH Q2A and Q2B guidances.

Expiry – it does not appear to be justified to grant a 2 year expiry based on (b) (4) months of stability data. This is what the applicant is requesting in section 3.2.P.8.1.2. This will be a review issue.

The applicant should provide for each (b) (4) color (Blue #1, Red #33) an FDA certificate of batch certification for a batch used for NDA batches of drug product.

Since the drug formulation contains significant levels of excipients (b) (4) provide data and controls for container closure component extractables (b) (4), and for leachables (b) (4). Alternatively, provide a data based justification for a lack of controls for extractables and leachables. For any extractables and leachables which were identified, provide a safety assessment of such extractables and leachables.

The applicant needs to clarify the specifications for the drug product in section 3.2.P.5.1, which contains an assay for pseudoephedrine hydrochloride and its impurities. This appears to be an error as there is no other indication in the NDA that the drug product is supposed to contain pseudoephedrine.

See filing check list above for additional comments.

Some of the COAs in this NDA may not be fully legible due to handwritten entries: this should be evaluated by the reviewer and legible replacement pages should be requested as necessary.

Recommendation:

NDA is suitable for filing from a CMC perspective.

Comments for filing letter:

Provide methods validation data for relevant non-compendial methods (e.g., chromatographic methods, microbiological assays) as per the ICH Q2A and Q2B guidances.

Provide for each (b) (4) color (Blue #1, Red#33) an FDA certificate of batch certification for a batch used for NDA batches of drug product.

Since the drug formulation contains significant levels of excipients (b) (4) provide data and controls for container closure component extractables (b) (4) and for leachables (b) (4). Alternatively, provide a data based justification for a lack of controls for extractables and leachables. For any extractables and leachables which were identified, provide a safety assessment of such extractables and leachables.

Provide 100% size color mockups of each actual carton and immediate container label.

Clarify that the formulation of drug product used for the clinical/bio studies was the same as that proposed for marketing.

Clarify the specifications for the drug product in section 3.2.P.5.1, which contains an assay for pseudoephedrine hydrochloride and its impurities. This appears to be an error.

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

We note that the proposed shelf life is 24 months even though you have provided (b) (4) months of real time data. As per the ICH Q1A guidance, a maximum of (b) (4) months shelf life may be granted provided the stability data are robust.

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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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ALAN C SCHROEDER

01/11/2011

It is the CMC recommendation that this NDA may be filed.

PRASAD PERI

01/11/2011

I concur