

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22279Orig1s000**

**CHEMISTRY REVIEW(S)**

# **Chemistry Review Cover Sheet**

**NDA 22279**

**Hycofenex**

**Hydrocodone Bitartrate,  
Pseudoephedrine Hydrochloride  
and Guaifenesin Oral Solution**

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

**OPQ/ONDP/DNDPII/NDPBIV**

**Reviewed for DPARP**

# Chemistry Review Data Sheet

1. NDA 22279
2. REVIEW #6
3. REVIEW DATE: April 24, 2015
4. REVIEWER: Arthur B. Shaw, Ph.D.
5. PREVIOUS DOCUMENTS: See Chem. Review #5
6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date	Comment
Complete Response	12/02/2014	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: Hycofenex
  - b) Non-Proprietary Name (USAN): Hydrocodone Bitartrate, Pseudoephedrine Hydrochloride 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/decongestant/expectorant
11. DOSAGE FORM: Solution
12. STRENGTH/POTENCY: 2.5 mg hydrocodone bitartrate/30.0 mg pseudoephedrine hydrochloride/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): None
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT: See Chem. Review #1
17. RELATED/SUPPORTING DOCUMENTS:

Chemistry Review #6 NDA 22279

**A. DMFs:**

Reviewed: **ACCEPTABLE**

DMF	Holder	DMF Subject	Review Date
		(b) (4)	Adequate 09/19/2014
			Adequate 03/12/2015
			Adequate for current process. IR sent for revised process. 04/21/2015

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:**

IND (b) (4)

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 April 24, 2015.

## The Chemistry Review for NDA 22279

### I. Recommendations

1. **Recommendation and Conclusion on Approvability:** The application maybe approved from a CMC point of view. All manufacturing and testing sites have been found Acceptable on April 24, 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), Pseudoephedrine HCl (PS) and Guaifenesin (GU) are USP items and their properties and synthesis have been assessed many times to support many applications. They are provided by three manufacturers, HC by (b) (4) (DMF (b) (4)), PS by (b) (4) (DMF (b) (4)), and GU (DMF (b) (4)) by (b) (4). The DMFs have been recently reviewed and found acceptable.

There had been a concern that the levels of (b) (4) in the HC were too high 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, whose components are all GRAS.

The applicant submitted testing and validation for *Burkholderia cepacia*, which was found acceptable in a Microbiology Quality Review dated 01/16/2015 (in Panorama).

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 for the symptomatic relief of cough (b) (4) nasal congestion (b) (4) and to (b) (4) loosen (b) (4) mucus (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**

Arthur B.  
Shaw -S



Digitally signed by Arthur B. Shaw -S  
DN: c=US, o=U.S. Government, ou=HHS,  
ou=FDA, ou=People, cn=Arthur B. Shaw -S,  
0.9.2342.19200300.100.1.1=1300057581  
Date: 2015.04.30 11:09:11 -04'00'

Julia C.  
Pinto -A



Digitally signed by Julia C. Pinto -A  
DN: c=US, o=U.S. Government, ou=HHS,  
ou=FDA, ou=People, cn=Julia C. Pinto -A,  
0.9.2342.19200300.100.1.1=1300366849  
Date: 2015.05.05 15:51:31 -04'00'

**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 #3**

**S DRUG SUBSTANCE [Guaifenesin, (b) (4)] ACCEPTABLE See Chem. Review #3**

**S DRUG SUBSTANCE [pseudoephedrine hydrochloride, (b) (4)]  
 ACCEPTABLE See Chem. Review #3**

**P DRUG PRODUCT**

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

**ACCEPTABLE See Chem. Review #3**

**P.2 Pharmaceutical Development: ACCEPTABLE See Chem. Review #3**

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

**P.3.1 Manufacturers**

Site	Function	Inspection Status from Panorama	
		Status	Date
Mikart Inc. 12090 Marietta Blvd Atlanta GA 30318 CFN 1050658	Manufacturing	Acceptable	04-24-2015
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 #5**

**P.3.3. Description of Manufacturing Process ACCEPTABLE See Chem. Review #3**

**P.3.4. Controls of Critical Steps and Intermediates ACCEPTABLE See Chem. Review #3**

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

**P.5 Control of Drug Product**

**P.5.1 Specification(s)**

Changes from Review #1

- Method name not included in specification
- Color (b) (4) violet (b) (4)
- Added test for *Burkholderia cepacia*, per request in CR letter.
- Change acceptance criteria for microbial tests

Chemistry Review #6 NDA 22279

Test	Original	Revised
Total Plate Count (TPC)	NMT (b) (4) CFUs	NMT (b) (4) CFU/mL
Total Combined Yeasts and Molds Count	NMT (b) (4) CFUs	NMT (b) (4) CFU/mL
E. Coli	(b) (4)	Absent

These changes are **ACCEPTABLE**

Test	Limits
Appearance	Meets Description (A transparent liquid with a (b) (4) color that has a black raspberry smell. No solid matter is visible.)
pH	(b) (4)
Specific Gravity	(b) (4)
<b>Identification (HPLC Retention Times)</b>	
- Hydrocodone Bitartrate 2 1/2 Hydrate	Retention time meets standard
- Pseudoephedrine Hydrochloride	Retention time meets standard
- Guaifenesin	Retention time meets standard
<b>Assay and Impurities</b>	
- Hydrocodone Bitartrate 2 1/2 Hydrate	(b) (4) %
(b) (4)	NMT (b) (4) %
- Other Individual Impurity	NMT %
- Total Impurities	NMT %
Guaifenesin	(b) (4) %
(b) (4)	NMT (b) (4) %
(b) (4)	NMT %
- Other Individual Impurity	NMT %
- Total impurities	NMT (b) (4) %
Pseudoephedrine HCl	(b) (4) %
(b) (4)	NMT (b) (4) %
- Total Impurities	NMT %
Methylparaben	(b) (4) %
Propylparaben	(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
- E. Coli	Absent
- Burkholderia cepacia	Absent

**ACCEPTABLE**

**P.5.2 Analytical Procedures ACCEPTABLE See Chem. Review #3**

**P.5.3 Validation of Analytical Procedures ACCEPTABLE See Chem. Review #3**

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

**P.5.6 Justification of Specification(s) ACCEPTABLE See Chem. Review #3**

**P.6 Reference Standards or Materials ACCEPTABLE See Chem. Review #3**

**P.7 Container Closure System: ACCEPTABLE See Chem. Review #3**

**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 #3**

**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 Additional comments to be communicated with the applicant as new material is received.**

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

# **Chemistry Review Cover Sheet**

**NDA 22279**

**Hydrocodone Bitartrate,  
Pseudoephedrine Hydrochloride  
and Guaifenesin Oral Solution**

**Arthur B. Shaw, Ph.D.  
ONDQA/DNDQA3/DAARP**

# Chemistry Review Data Sheet

1. NDA 22279
2. REVIEW #5
3. REVIEW DATE: November 4, 2011
4. REVIEWER: Arthur B. Shaw, Ph.D.
5. PREVIOUS DOCUMENTS: See Chem. Review #4
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>	<u>Comment</u>
Complete Response	18Jul-2011	Class 2 Resubmission

7. NAME & ADDRESS OF APPLICANT AND AGENT:

Applicant  
 Name: MIKART INC  
 Address: Chattahoochee Avenue  
 Atlanta, GA 30318

Note that the applicant was changed from the previous owner, (b) (4) Mikart in a letter dated October 24, 2011.

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Hydrocodone Bitartrate, Pseudoephedrine Hydrochloride and Guaifenesin Oral Solution
- b) Non-Proprietary Name (USAN): Hydrocodone Bitartrate, Pseudoephedrine Hydrochloride 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/decongestant/expectorant

11. DOSAGE FORM: Solution

12. STRENGTH/POTENCY: 2.5 mg hydrocodone bitartrate/30.0 mg pseudoephedrine hydrochloride/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): 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 08/15/2011
			Adequate 10/24/2011
			IR 11/04/2011
			Adequate 10/06/08

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

Note that the hydrocodone bitartrate reference product used for the BE studies was Morton Grove's Hydrocodone Bitartrate/Homatropine Methylbromide (ANDA 88-088). A copy of the label was provided in Attachment I of the September 16, 2010 amendment.

**B. Other Documents:**

IND (b) (4)

## 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:
  - The original drug product manufacturing, testing, and labeling site (b) (4) has closed and is not available for inspection. Therefore the Office of Compliance recommend Withhold on (b) (4).
  - Mikart Laboratories has been identified as the new manufacturing and testing site for the drug product. The inspection result is Acceptable (b) (4).

## The Chemistry Review for NDA 22279

### I. Recommendations

#### 1. Recommendation and Conclusion on Approvability

The NDA is recommended for Complete response from a CMC perspective at this time due to Microbiology issues (inadequate controls on *Burkholderia cepacia*). All sites have a satisfactory CGMP inspection.

#### 2. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable. Submit updated stability data as a CBE-30 Supplement.

### 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), Pseudoephedrine HCl (PS) and Guaifenesin (GU) are USP items and their properties and synthesis have been assessed many times to support many applications. They are provided by three manufacturers, HC by (b) (4) (DMF (b) (4)), PS by (b) (4) (DMF (b) (4)), and GU (DMF (b) (4)) by (b) (4). The DMFs have been recently reviewed and found acceptable. However the new owner of the application, Mikart, Inc., has not provided copies of the LOAs in the application.

There had been a concern that the levels of (b) (4) in the HC were too high 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 as described for the original manufacturer (b) (4) are straightforward. All of the excipients are compendial except the colors, which are FD&C and D&C colors, and the flavoring, whose components are all GRAS. The new manufacturer, Mikart, employs the same manufacturing procedure and components as reviewed previously. The specifications are not adequate to control the drug product due to inadequate microbiological quality testing. There is no test or acceptance criterion for *Burkholderia cepacia*. The New Drug Microbiology Staff reviewers have identified this microorganism as requiring adequate control for aqueous-based oral solutions.

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 period for the original product manufactured by the original applicant. A new batch manufactured by the new manufacturer using the same formulation and manufacturing procedure showed no degradation over 90 days under accelerated conditions and six

months at room temperature conditions. 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 for the symptomatic relief of cough (b) (4) nasal congestion (b) (4) and to (b) (4) loosen (b) (4) mucus (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. Control of the microbial quality of the drug product, an oral aqueous-based liquid, is not adequate.

**III. Administrative**

See DFS signatures and cc's

**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 #3**

**S DRUG SUBSTANCE [Guaifenesin, (b) (4)] ACCEPTABLE See Chem. Review #3**

**S DRUG SUBSTANCE [pseudoephedrine hydrochloride, (b) (4)] ACCEPTABLE See Chem. Review #3**

**P DRUG PRODUCT [Mikart]**

**P.1 Description and Composition of the Drug Product [Mikart] ACCEPTABLE See Chem. Review #3**

**P.2 Pharmaceutical Development: [Mikart] ACCEPTABLE See Chem. Review #3**

**P.3. Manufacture [Mikart] ACCEPTABLE See Chem. Review #1**

**P.3.1 Manufacturers [Mikart]**

Site	Function	Inspection Status from EES		
		Status	Basis	Date
Mikart Inc. 12090 Marietta Blvd Atlanta GA 30318 CFN 1050658	Manufacturing	Acceptable	District Recommendation	03-Jan-2011
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	OC Recommendation based on Profile	(b) (4)

**P.3.2 Batch Formula [Mikart]**

The applicant has provided a proposed production batch formula for a (b) (4) batch.

Proposed Production Batch Formula (b) (4)			
Component	Reference	Quantity Per Batch	
<b>Actives</b>			
Hydrocodone Bitartrate USP	USP	(b) (4)	
Guaifenesin USP	USP		
Pseudoephedrine Hydrochloride USP	USP		
<b>Inactives</b>			
Sorbitol (b) (4) USP	USP		
Glycerin USP	USP		
Saccharin Sodium USP	USP		
Polyethylene Glycol (b) (4) NF	NF		
(b) (4) Black Raspberry Flavor (b) (4)	N/A		
FD&C Blue #1 (b) (4)	N/A		
D&C Red #33 (b) (4)	N/A		
Methylparaben NF	NF		
Propylparaben NF	NF		
Citric Acid (b) (4) USP	USP		
Sodium Citrate USP	USP		
Purified Water USP	USP		
Total			

A comparison with the batch formula for the (b) (4) scale shows a number of discrepancies due to the incorrect choice of units (kg instead of g)

Ingredient	(b) (4)
Hydrocodone Bitartrate USP	
Guaifenesin USP	
Pseudoephedrine Hydrochloride USP	
Sorbitol (b) (4) USP	
Glycerin USP	
Saccharin Sodium	
Polyethylene Glycol (b) (4) NF	
(b) (4) Black Raspberry Flavor (b) (4)	
FD & C Blue #1	
D & C Red #33	
Methylparaben NF	
Propylparaben NF	
Citric Acid (b) (4) USP	
Sodium Citrate (b) (4) US	
Purified Water USP	

However the actual batch production record shows the correct units.

Chemistry Review #5 NDA 22279

BILL OF MATERIALS

#	CODE	RAW MATERIAL NAME	QUANTITY	OVER-AGE	FORMULA (b) (4)
1.	(b) (4)	Hydrocodone Bitartrate USP ①			
2.		Guaifenesin USP ②			
3.		Pseudoephedrine Hydrochloride USP ③			
4.		Sorbitol (b) (4) USP			
5.		Glycerin USP			
6.		Saccharin Sodium USP			
7.		Polyethylene Glycol (b) (4) NF			
8.		(b) (4) Black Raspberry Flavor (b) (4)			
9.		FD&C Blue #1 (b) (4)			
10.		D&C Red #33 (b) (4)			
11.		Methylparaben NF			
12.		Propylparaben NF			
13.		Citric Acid (b) (4) USP			
14.		Sodium Citrate USP			
15.		Purified Water USP (b) (4)			

ACCEPTABLE

*P.3.3. Description of Manufacturing Process [Mikart] ACCEPTABLE See Chem. Review #3*

*P.3.4. Controls of Critical Steps and Intermediates [Mikart] ACCEPTABLE See Chem.*

**Review #3**

**P.4 Control of Excipients [Mikart]**

All excipients are compendial except for the colors and the flavor. These are **ACCEPTABLE**  
See Chem. Review #1

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/s/  
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ARTHUR B SHAW  
11/04/2011

PRASAD PERI  
11/04/2011  
I concur

**NDA 22279**  
**Hydrocodone Bitartrate, Pseudoephedrine Hydrochloride and**  
**Guaifenesin Oral Solution**

(2.5 mg hydroxycodone bitartrate/30.0 mg pseudoephedrine hydrochloride/200 mg  
guaifenesin per 5 mL)

**Summary of the Basis for the Recommended Action  
from Chemistry, Manufacturing, and Controls**

**Applicant:**

(b) (4)

**Indication:**

For the symptomatic relief of cough (b) (4) nasal  
congestion (b) (4) and to (b) (4) loosen (b) (4) mucus (b) (4)

**Dosage Regimen**

Adults (b) (4): Two teaspoonfuls (10  
mL) every 4 hours, not to exceed 4 doses in 24 hours.

(b) (4)

**Presentations:**

The Oral Solution is packaged in white (b) (4) HDPE bottles ((b) (4) mL) and  
white (b) (4) HDPE bottles ((b) (4) mL). All bottles are capped with child  
resistant containers.

**EER Status:**

**Correction: Note the previous secondary review concluded that the drug  
product manufacturing site had a withhold status. Actually the withhold  
status has been provided to the applicant holder (b) (4)**  
**This is likely due to their association with (b) (4) (u) (4) which  
received a warning letter. More information will be provided by the Office  
of Compliance in the weeks ahead.** The applicant site was found to have a  
**withhold status as of (b) (4)**. Note that the original drug product  
manufacturing site was dismantled and sold leading to a withhold  
recommendation by the office of Compliance.

**Consults:**

**EA – Granted**  
**Methods Validation –** Revalidation by Agency will not be requested since the  
methods listed are standard.  
**Pharmacology/Toxicology –** Acceptable.  
**Biopharmaceutics –** Not applicable  
**Quality Microbiology –** Acceptable.

**Original Submission:** 22-Aug-2008 (Action taken 6/22/2009)

**Resubmission:** 22-Jul-2010

**Post-Approval CMC Commitments:** None

**Outstanding issues:**

**All sites should have an acceptable recommendation from the Office of Compliance.**

**Additional Items:**

Drug Master Files are acceptable or the pertinent information has been adequately provided in the application.

Method validation will not be requested since all methods are standard.

**Overall Conclusion:**

From a CMC perspective, the application is recommended for a **complete response**.

The proposed name [REDACTED]<sup>(b) (4)</sup> was not found acceptable by DMEPA. An alternative name of [REDACTED]<sup>(b) (4)</sup> was also reviewed and not found acceptable by DMEPA.

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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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PRASAD PERI  
01/31/2011

**NDA 22279**  
**Hydrocodone Bitartrate, Pseudoephedrine Hydrochloride and**  
**Guaifenesin Oral Solution**

(2.5 mg hydroxycodone bitartrate/30.0 mg pseudoephedrine hydrochloride/200 mg  
guaifenesin per 5 mL)

**Summary of the Basis for the Recommended Action  
from Chemistry, Manufacturing, and Controls**

**Applicant:**

(b) (4)

**Indication:**

For the symptomatic relief of cough (b) (4) nasal  
congestion (b) (4) and to (b) (4) loosen (b) (4) mucus (b) (4)

**Dosage Regimen**

Adults (b) (4): Two teaspoonfuls (10  
mL) every 4 hours, not to exceed 4 doses in 24 hours.

**Presentations:**

The Oral Solution is packaged in white (b) (4) HDPE bottles (b) (4) mL) and  
white (b) (4) HDPE bottles (b) (4) mL). All bottles are capped with child  
resistant containers.

**EER Status:**

The drug product manufacturing site was found to have a **withhold status as off**  
(b) (4) Note that the original drug product manufacturing site was  
dismantled and sold leading to a withhold recommendation by the office of  
Compliance.

**Consults:**

**EA** – Granted  
**Methods Validation** – Revalidation by Agency will not be requested since the  
methods listed are standard.  
**Pharmacology/Toxicology** – Acceptable.  
**Biopharmaceutics** – Not applicable  
**Quality Microbiology** – Acceptable.

**Original Submission:** 22-Aug-2008 (Action taken 6/22/2009)

**Resubmission:** 22-Jul-2010

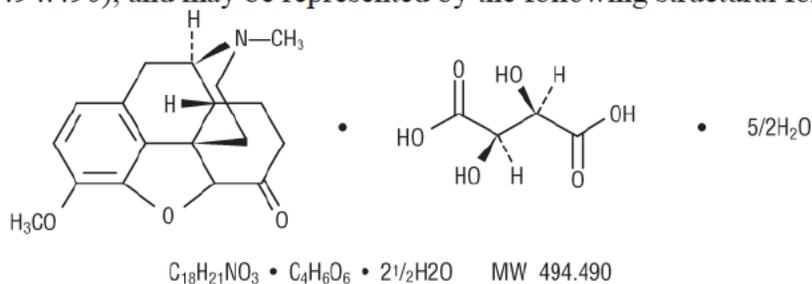
**Post-Approval CMC Commitments:** None

**Drug Substances:** The drug substances, Hydrocodone Bitartrate (HC), Pseudoephedrine HCl  
(PS) and Guaifenesin (GU) are USP items and their properties and synthesis have been assessed

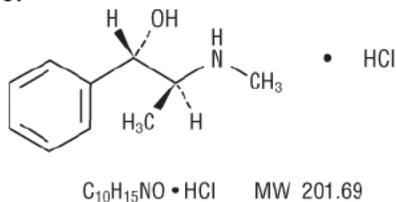
many times to support many applications. They are provided by three manufacturers, HC by (b) (4)

The DMFs have been recently reviewed and found acceptable. There had been a concern that the levels of (b) (4) in the HC were too high 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.

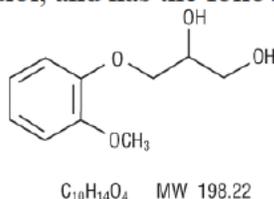
**Hydrocodone bitartrate** is Morphinan-6-one, 4,5-epoxy-3-methoxy-17-methyl-, (5)-, [*R*\*,*R*\*]-2,3-dihydroxybutanedioate (1:1), hydrate (2:5); also known as 4,5-Epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5), and a fine white crystal or crystalline powder, which is derived from the opium alkaloid, thebaine, has a molecular weight of (494.490), and may be represented by the following structural formula:



**Pseudoephedrine hydrochloride** is an adrenergic (vasoconstrictor) agent with the chemical name (1*S*,2*S*)-2-methylamino-1-phenyl-1-propanol hydrochloride, and Benzenemethanol, -[1-(methylamino)ethyl]-, [*S*-(*R*\*,*R*\*)]-, hydrochloride. Pseudoephedrine hydrochloride occurs as fine, white to off-white crystals or powder, having a faint characteristic odor. It is very soluble in water, freely soluble in alcohol, and sparingly soluble in chloroform. It has the following chemical structure:



**Guaifenesin** is 1,2-Propanediol, 3-(2-methoxyphenoxy)-, (±)-; also known as (±)-3-(*o*-Methoxyphenoxy)-1,2-propanediol, and has the following chemical structure:



Hydrocodone bitartrate is tested for appearance, identification by IR and UV, specific rotation, pH, loss on drying, heavy metals, residue on ignition, chloride content, assay, related substances, and residual solvents. The container closure referenced to the DMF but is stored in (b) (4).

Hydrocodone bitartrate is manufactured by (b) (4). The applicant's retest period is (b) (4).

Pseudoephedrine hydrochloride is tested as per USP for appearance, identification by IR, melting range, specific rotation, pH, loss on drying, residue on ignition, ordinary impurities and organic volatile impurities, residual solvents, and assay. The container closure referenced to the DMF but is stored in (b) (4). Pseudoephedrine hydrochloride is manufactured by (b) (4). The applicant's retest period is (b) (4).

Guaifenesin is also tested as per USP for assay, description, identification (IR and UV), melting range, loss on drying, heavy metals, chromatographic purity, and heavy metals. It is manufactured by (b) (4). The applicant's retest period is (b) (4).

**Conclusion:** The drug substances are acceptable.

**Drug Product:**

The drug product is a transparent purple colored liquid with a raspberry smell. The manufacturing process and controls as described for the original manufacturer ( (b) (4) ) are straightforward. All of the excipients are compendial except the colors, which are FD&C and D&C colors, and the flavoring, whose components are all GRAS. The excipients are sorbitol, glycerin, polyethylene glycol, methylparaben, propylparaben, citric acid, sodium citrate, sodium saccharin, black raspberry flavor, D&C Red #33, FD&C Blue #1, and purified water. The specifications are adequate to control the drug product, including tests for all the drug substances and their impurities. The drug product is very stable, showing no changes in any of the tested parameters, including degradants, over the 24 months reporting period for the original product manufactured by the original applicant. Since the original drug product manufacturer was dismantled and sold off during the NDA review cycle, a new batch was manufactured by the new manufacturer (Mikart) using the same formulation and manufacturing procedure compared to the original drug product made by (b) (4), showed no degradation over six months under accelerated and room temperature conditions. Therefore an expiration period of **24 months** is acceptable.

The proposed specifications for the drug product include appearance, pH, specific gravity, assay, impurities (individually and total for hydrocodone, pseudoephedrine, guaifenesin), assay for methylparaben, assay for propylparaben, microbial testing, and preservative effectiveness testing.

The proposed drug product is manufactured, packaged and tested by Mikart Inc. in Atlanta, GA. Microbial limits testing are performed by (b) (4). The manufacturing scale used for the registration batches was (b) (4) the applicant has proposed increasing the scale to (b) (4) for commercial manufacturing.

**Conclusion:** The drug product is acceptable.

**Outstanding issues:**

**All sites should have an acceptable recommendation from the Office of Compliance.**

**Additional Items:**

Drug Master Files are acceptable or the pertinent information has been adequately provided in the application.

Method validation will not be requested since all methods are standard.

**Overall Conclusion:**

From a CMC perspective, the application is recommended for a **complete response**.

The proposed name (b) (4) was not found acceptable by DMEPA. An alternative name of (b) (4) was also reviewed and not found acceptable by DMEPA.



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/s/  
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PRASAD PERI

01/07/2011

Complete response until all sites are acceptable as per Office of Compliance.

# **Chemistry Review Cover Sheet**

**NDA 22279**

**Hydrocodone Bitartrate,  
Pseudoephedrine Hydrochloride  
and Guaifenesin Oral Solution**

**Arthur B. Shaw, Ph.D.  
ONDQA/DNDQA3/DAARP**

# Chemistry Review Data Sheet

1. NDA 22279
2. REVIEW #4
3. REVIEW DATE: January 3, 2011
4. REVIEWER: Arthur B. Shaw, Ph.D.
5. PREVIOUS DOCUMENTS: See Chem. Review #3
6. SUBMISSION(S) BEING REVIEWED:  
Inspection completed.
7. NAME & ADDRESS OF APPLICANT AND AGENT:

Applicant  
Name:  (b) (4)  
Address: 

Agent  
Name Mikart Inc.  
Address: 1750 Chattahoochee Avenue  
Atlanta GA 30318

Contact Person at Agent  
Name Lisa Apolis  
Phone 404-351-4510  
Fax 404-352-0351  
E-mail [lapolis@mikart.com](mailto:lapolis@mikart.com)

8. DRUG PRODUCT NAME/CODE/TYPE:
  - a) Proprietary Name: Hydrocodone Bitartrate, Pseudoephedrine Hydrochloride and Guaifenesin Oral Solution
  - b) Non-Proprietary Name (USAN): Hydrocodone Bitartrate, Pseudoephedrine Hydrochloride 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/decongestant/expectorant
11. DOSAGE FORM: Solution
12. STRENGTH/POTENCY: 2.5 mg hydroxycodone bitartrate/30.0 mg pseudoephedrine hydrochloride/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): None

Chemistry Review #4 NDA 22279

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 11/08/2010 IR 11/08/2010 Response under review by M.Manzoni
			Adequate 11/01/2010 IR 11/03/2010 No response
			Adequate 10/06/08 Yon de Lu Subsequent updates contain no significant new information. NAI'ed in DARRTS

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

Note that the hydrocodone bitartrate reference product used for the BE studies was Morton Grove's Hydrocodone Bitartrate/Homatropine Methylbromide (ANDA 88-088). A copy of the label was provided in Attachment I of the September 16, 2010 amendment.

**B. Other Documents:**

IND (b) (4)

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:

The original drug product manufacturing, testing, and labeling site (b) (4) has closed and is not available for inspection. Therefore the Office of Compliance recommend Withhold on (b) (4).

Mikart Laboratories has been identified as the new manufacturing and testing site for the drug product. The inspection result is Acceptable ( (b) (4) ).

**The Chemistry Review for NDA 22279**

**I. Recommendations**

**1. Recommendation and Conclusion on Approvability**

The NDA may be approved from the CMC perspective at this time. All sites have a satisfactory CGMP inspection.

**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), Pseudoephedrine HCl (PS) and Guaifenesin (GU) are USP items and their properties and synthesis have been assessed many times to support many applications. They are provided by three manufacturers, HC (b) (4)

(b) (4) The DMFs have been recently reviewed and found acceptable. There had been a concern that the levels of (b) (4) in the HC were too high 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 liquid so there is no issue regarding dissolution. The manufacturing process and controls as described for the original manufacturer (b) (4) are straightforward. All of the excipients are compendial except the colors, which are FD&C and D&C colors, and the flavoring, whose components are all GRAS, The specifications are adequate to control the drug product, including tests for all the drug substances and their impurities. The drug product is very stable, showing no changes in any of the tested parameters, including degradants, over the 24 months reporting period for the original product manufactured by the original applicant. A new batch manufactured by the new manufacturer using the same formulation and manufacturing procedure showed no degradation over six months under accelerated and room temperature conditions. 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 for the symptomatic relief of cough (b) (4) nasal congestion (b) (4) and to (b) (4) loosen (b) (4) mucus (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 and the drug product are adequately described to provide adequate quality for the intended use.

**III. Administrative**

See DFS signatures and cc's

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

- S DRUG SUBSTANCE [Hydrocodone bitartrate, (b) (4)]**
- S.1 General Information [Hydrocodone bitartrate, (b) (4)]: ACCEPTABLE See Chem. Review #1**
- S.2 Manufacture [Hydrocodone bitartrate, (b) (4)]: ACCEPTABLE See DMF (b) (4)**
- S.3 Characterization [Hydrocodone bitartrate, (b) (4)] ACCEPTABLE See DMF (b) (4)**
- S.4 Control of Drug Substance [Hydrocodone bitartrate, (b) (4)]**
- S.4.1 Specifications [Hydrocodone bitartrate, (b) (4)] ACCEPTABLE See Chem. Review #3**
- S.4.2 Analytical Procedures [Hydrocodone bitartrate, (b) (4)] ACCEPTABLE See Chem. Review #3**
- S.4.3 Validation of Analytical Procedures [Hydrocodone bitartrate, (b) (4)] ACCEPTABLE See Chem. Review #3**
- S.4.4 Batch Analysis [Hydrocodone bitartrate, (b) (4)] ACCEPTABLE See Chem. Review #3**
- S.4.5 Justification of Specification [Hydrocodone bitartrate, (b) (4)]: ACCEPTABLE See Chem. Review #3**
- S.6 Container Closure System [Hydrocodone bitartrate, (b) (4)]: ACCEPTABLE See DMF (b) (4)**
- S.7 Stability [Hydrocodone bitartrate, (b) (4)]: ACCEPTABLE See DMF (b) (4)**
- S DRUG SUBSTANCE [Guaifenesin, (b) (4)]**
- S.1 General Information [Guaifenesin, (b) (4)]: ACCEPTABLE See Chem. Review #1**
- S.2 Manufacture [Guaifenesin, (b) (4)]: ACCEPTABLE See DMF (b) (4)**
- S.3 Characterization [Guaifenesin, (b) (4)] ACCEPTABLE See DMF (b) (4)**
- S.4 Control of Drug Substance [Guaifenesin, (b) (4)]**
- S.4.1 Specifications [Guaifenesin, (b) (4)] ACCEPTABLE See Chem. Review #3**
- S.4.2 Analytical Procedures [Guaifenesin, (b) (4)] ACCEPTABLE See Chem. Review #3**
- S.4.3 Validation of Analytical Procedures [Guaifenesin, (b) (4)] ACCEPTABLE See Chem. Review #3**
- S.4.4 Batch Analysis [Guaifenesin, (b) (4)] ACCEPTABLE See Chem. Review #3**
- S.4.5 Justification of Specification [Guaifenesin, (b) (4)]: ACCEPTABLE See Chem. Review #3**

- S.6 Container Closure System [Guaifenesin, (b) (4)]: ACCEPTABLE See DMF (b) (4)
- S.7 Stability [Guaifenesin, (b) (4)]: ACCEPTABLE See DMF (b) (4)

**S DRUG SUBSTANCE** [pseudoephedrine hydrochloride, (b) (4)]  
S.1 General Information [pseudoephedrine hydrochloride, (b) (4)]:  
ACCEPTABLE See Chem. Review #1

S.2 Manufacture [pseudoephedrine hydrochloride, (b) (4)]: ACCEPTABLE See DMF (b) (4)

S.3 Characterization [pseudoephedrine hydrochloride, (b) (4)] ACCEPTABLE See DMF (b) (4)

S.4 Control of Drug Substance [pseudoephedrine hydrochloride, (b) (4)]

S.4.1 Specifications [Pseudoephedrine hydrochloride, (b) (4)] ACCEPTABLE See Chem. Review #3

S.4.2 Analytical Procedures [Pseudoephedrine hydrochloride, (b) (4)] ACCEPTABLE See Chem. Review #3

S.4.3 Validation of Analytical Procedures [Pseudoephedrine hydrochloride, (b) (4)] ACCEPTABLE See Chem. Review #3

S.4.4 Batch Analysis [Pseudoephedrine hydrochloride, (b) (4)] ACCEPTABLE See Chem. Review #3

S.4.5 Justification of Specification [Pseudoephedrine hydrochloride, (b) (4)]:  
ACCEPTABLE See Chem. Review #3

S.6 Container Closure System [pseudoephedrine hydrochloride, (b) (4)]:  
ACCEPTABLE See DMF (b) (4)

S.7 Stability [pseudoephedrine hydrochloride, (b) (4)]: ACCEPTABLE See DMF (b) (4)

**P DRUG PRODUCT** [Mikart]

P.1 Description and Composition of the Drug Product [Mikart]  
ACCEPTABLE See Chem. Review #3

P.2 Pharmaceutical Development: [Mikart] ACCEPTABLE See Chem. Review #3

P.3 Manufacture [Mikart] ACCEPTABLE See Chem. Review #1

**P.3.1 Manufacturers [Mikart]**

Site	Function	Inspection Status from EES		
		Status	Basis	Date
Mikart Inc. 12090 Marietta Blvd Atlanta GA 30318 CFN 1050658	Manufacturing	Acceptable	District Recommendation	03-Jan- 2011
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)		Acceptable	OC Recommendation based on Profile	(b) (4)

**P.3.2 Batch Formula [Mikart] ACCEPTABLE See Chem. Review #3****P.3.3. Description of Manufacturing Process [Mikart] ACCEPTABLE See Chem. Review #3****P.3.4. Controls of Critical Steps and Intermediates [Mikart] ACCEPTABLE See Chem. Review #3****P.4 Control of Excipients [Mikart]**

All excipients are compendial except for the colors and the flavor. These are **ACCEPTABLE**  
See Chem. Review #1

**P.5 Control of Drug Product [Mikart]****P.5.1 Specification(s) ACCEPTABLE See Chem. Review #3****P.5.2 Analytical Procedures ACCEPTABLE See Chem. Review #3****P.5.3 Validation of Analytical Procedures ACCEPTABLE See Chem. Review #3****P.5.5. Characterization of Impurities ACCEPTABLE See Chem Review #1****P.5.6 Justification of Specification(s) ACCEPTABLE See Chem. Review #3****P.6 Reference Standards or Materials ACCEPTABLE See Chem. Review #3****P.7 Container Closure System: ACCEPTABLE See Chem. Review #3****P.8 Stability [Mikart]****P.8.1 Stability Summary and Conclusions ACCEPTABLE See Chem. Review #3****P.8.2 Post-approval Stability Protocol and Stability Commitment ACCEPTABLE See Chem. Review #3**

***P.8.3 Stability Data ACCEPTABLE See Chem. Review #3***

**A APPENDICES N/A**

**R REGIONAL INFORMATION [Mikart]**

**R1 Executed Batch Records. [Mikart] ACCEPTABLE**

**R2 Comparability Protocol N/A**

**R3 Methods Validation Package N/A**

**II. LABELING [Mikart] ACCEPTABLE See Chem. Review #1**

Chemistry Review #4 NDA 22279

<p><b>1, This review contains new information added to the table below: <input checked="" type="checkbox"/> Yes;</b> <b><input type="checkbox"/> No</b></p> <p>Review date: _____</p>
<p>2) Are any nanoscale materials included in this application? (If yes, please proceed to the next questions.) Yes _____; No <input checked="" type="checkbox"/> ; Maybe (please specify) _____</p>

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/s/  
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ARTHUR B SHAW

01/03/2011

Approved from CMC point of view. All inspections acceptable

PRASAD PERI

01/03/2011

I Concur

# **Chemistry Review Cover Sheet**

**NDA 22279**

**Hydrocodone Bitartrate,  
Pseudoephedrine Hydrochloride  
and Guaifenesin Oral Solution**

**Arthur B. Shaw, Ph.D.  
ONDQA/DNDQA3/DAARP**

# Chemistry Review Data Sheet

1. NDA 22279
2. REVIEW #3
3. REVIEW DATE: December 24, 2010
4. REVIEWER: Arthur B. Shaw, Ph.D.
5. PREVIOUS DOCUMENTS: See Chem. Review #2
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>	<u>Comment</u>
Complete Response	22-Jul-2010	Class 2 Resubmission
IR e-mail	13-Aug-2010	Request for a list of changes in resubmission
Amendment	18-Aug-2010	Response to 13-Aug-2010 e-mail
IR e-mail	20-Aug-2010	Request name and manufacturing information for comparator products
Amendment	23-Aug-2010	Response to 20-Aug-2010 e-mail
Amendment	20-Dec-2010	Updated Stability information

7. NAME & ADDRESS OF APPLICANT AND AGENT:

Applicant  
Name:  (b) (4)  
Address: 

Agent  
Name Mikart Inc.  
Address: 1750 Chattahoochee Avenue  
Atlanta GA 30318

Contact Person at Agent  
Name Lisa Apolis  
Phone 404-351-4510  
Fax 404-352-0351  
E-mail [lapolis@mikart.com](mailto:lapolis@mikart.com)

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Hydrocodone Bitartrate, Pseudoephedrine Hydrochloride and Guaifenesin Oral Solution
- b) Non-Proprietary Name (USAN): Hydrocodone Bitartrate, Pseudoephedrine Hydrochloride 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/decongestant/expectorant

11. DOSAGE FORM: Solution

12. STRENGTH/POTENCY: 2.5 mg hydroxycodone bitartrate/30.0 mg pseudoephedrine hydrochloride/200 mg guaifenesin per 5 mL

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:   X   Rx        OTC

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 11/08/2010 IR 11/08/2010 Response under review by M.Manzoni
			Adequate 11/01/2010 IR 11/03/2010 No response
			Adequate 10/06/08 Yon de Lu Subsequent updates contain no significant new information. NAI'ed in DARRTS

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

Note that the hydrocodone bitartrate reference product used for the BE studies was Morton Grove's Hydrocodone Bitartrate/Homatropine Methylbromide (ANDA 88-088). A copy of the label was provided in Attachment I of the September 16, 2010 amendment.

**B. Other Documents:**

IND (b) (4)

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:

The original drug product manufacturing, testing, and labeling site (b) (4) has closed and is not available for inspection. Therefore the Office of Compliance recommend Withhold on (b) (4)

Mikart Laboratories has been identified as the new manufacturing and testing site for the drug product. The inspection result is Pending.

## The Chemistry Review for NDA 22279

### I. Recommendations

#### 1. Recommendation and Conclusion on Approvability

The NDA is approvable from the CMC perspective at this time. In order to approve the application all sites must have a satisfactory CGMP inspection. One site, the drug product manufacturing site, is pending.

#### 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), Pseudoephedrine HCl (PS) and Guaifenesin (GU) are USP items and their properties and synthesis have been assessed many times to support many applications. They are provided by three manufacturers, HC (b) (4)

(b) (4) The DMFs have been recently reviewed and found acceptable. There had been a concern that the levels of (b) (4) in the HC were too high 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 liquid so there is no issue regarding dissolution. The manufacturing process and controls as described for the original manufacturer (b) (4) are straightforward. All of the excipients are compendial except the colors, which are FD&C and D&C colors, and the flavoring, whose components are all GRAS. The specifications are adequate to control the drug product, including tests for all the drug substances and their impurities. The drug product is very stable, showing no changes in any of the tested parameters, including degradants, over the 24 months reporting period for the original product manufactured by the original applicant. A new batch manufactured by the new manufacturer using the same formulation and manufacturing procedure showed no degradation over six months under accelerated and room temperature conditions. 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 for the symptomatic relief of cough (b) (4) nasal congestion (b) (4) and to (b) (4) loosen (b) (4) mucus (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 and the drug product are adequately described to provide adequate quality for the intended use.

**III. Administrative**

See DFS signatures and cc's

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/s/  
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ARTHUR B SHAW  
12/24/2010

PRASAD PERI  
12/27/2010  
I concur

# **Chemistry Review Cover Sheet**

**NDA 22279**

**Hydrocodone Bitartrate,  
Pseudoephedrine Hydrochloride  
and Guaifenesin Oral Solution**

**Arthur B. Shaw, Ph.D.  
ONDQA/DPA1/DAARP**

# Chemistry Review Data Sheet

1. NDA 22279
2. REVIEW #2
3. REVIEW DATE: June 16, 2009
4. REVIEWER: Arthur B. Shaw, Ph.D.
5. PREVIOUS DOCUMENTS: See Chem. Review #1
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>	<u>Comment</u>
Amendment	21-Apr-2009	Change in sponsor to  (b) (4)
Amendment	24-Apr-2009	Change in drug product manufacturing and testing sites

7. NAME & ADDRESS OF APPLICANT AND AGENT:

Applicant  
Name:  (b) (4)  
Address: 

Agent  
Name Mikart Inc.  
Address: 1750 Chattahoochee Avenue  
Atlanta GA 30318

Contact Person at Agent  
Name Lisa Apolis  
Phone 404-351-4510  
Fax 404-352-0351  
E-mail [lapolis@mikart.com](mailto:lapolis@mikart.com)

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Hydrocodone Bitartrate, Pseudoephedrine Hydrochloride and Guaifenesin Oral Solution
- b) Non-Proprietary Name (USAN): Hydrocodone Bitartrate, Pseudoephedrine Hydrochloride 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/decongestant/expectorant

11. DOSAGE FORM: Solution

12. STRENGTH/POTENCY: 2.5 mg hydroxycodone bitartrate/30.0 mg pseudoephedrine hydrochloride/200 mg guaifenesin per 5 mL

13. ROUTE OF ADMINISTRATION: Oral

Chemistry Review #2 NDA 22279

14. Rx/OTC DISPENSED:  X  Rx   OTC

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 June 8, 2009
			Adequate needs IR letter 04/27/2009
			Adequate 10/06/08 Yon de Lu Recent updates contain no significant new information.

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

Note that the IR letter cannot be sent to (b) (4) until the DMF holder submits a new LOA authorizing Mikart to reference the DMF.

**B. Other Documents:**

IND (b) (4)

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:

One drug substance manufacturing site (b) (4) for pseudoephedrine HCl) had an inspection assigned but they state that they are not ready for inspection (EES, May 18, 2009). Therefore the Office of Compliance recommend Withhold on (b) (4).

The original drug product manufacturing, testing, and labeling site (b) (4) has closed and is not available for inspection. Therefore the Office of Compliance recommend Withhold on (b) (4)

(b) (4)

Mikart Laboratories has been identified as the new manufacturing and testing site for the drug product.

## The Chemistry Review for NDA 22279

### I. Recommendations

#### 1. Recommendation and Conclusion on Approvability

The NDA is approvable from the CMC perspective at this time. The quality information for the manufacturing site described in the application, (b) (4) cannot be used to support the quality of the drug product because, according to the amendment submitted on April 24, 2009, this site will not be used to manufacture drug product for the marketing of this drug. In order to approve the application, satisfactory quality information must be provided to the NDA for drug product manufactured at a new manufacturing site.

In addition all drug substance and drug product manufacturing sites must be in compliance with Current Good Manufacturing Practices.

#### 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), Pseudoephedrine HCl (PS) and Guaifenesin (GU) are USP items and their properties and synthesis have been assessed many times to support many applications. They are provided by three manufacturers, HC (b) (4)

(b) (4) The DMFs have been recently reviewed and found acceptable. There had been a concern that the levels of (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.

In addition the manufacturing site for the PS was not ready for inspection and therefore a Withhold recommendations was issued by the Office of Compliance.

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

As a result of new ownership of the NDA (see below), new letters of authorization form the drug substance DMF holders will be required.

##### 2. Drug Product

The drug product is an oral liquid so there is no issue regarding dissolution. The manufacturing process and controls as described for the original manufacturer (b) (4) are straightforward. All of the excipients are compendial except the colors, which are FD&C and D&C colors, and the flavoring, whose components are all GRAS, The specifications are adequate to control the drug product, including tests for all the drug substances and their impurities.. The drug product is very stable,

showing no changes in any of the tested parameters, including degradants, over the 12 months reporting period. Therefore an expiration period of 24 months is acceptable.

However since the NDA was recently sold to a new owner, (b) (4) and the new manufacturing and testing site, Mikart Inc. has been identified. However there is no information about the manufacturing and testing at the new site.

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

The drug product is intended to be used for the symptomatic relief of cough (b) (4) nasal congestion (b) (4), and to (b) (4) loosen (b) (4) mucus (b) (4). Each of these drug substances has been approved separately for their labeled uses.

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

The drug is not approvable because, although the CMC review shows that the drug can be manufactured consistently at the original site (b) (4) to deliver the labeled amount of drug with each dose, there is no information about any CMC information at the new manufacturing site.

**III. Administrative**

See DFS signatures and cc's

**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

S DRUG SUBSTANCE [pseudoephedrine hydrochloride, (b) (4)]  
 S.1 General Information [pseudoephedrine hydrochloride, (b) (4)]:  
 ACCEPTABLE See Chem. Review #1

S.2 Manufacture[pseudoephedrine hydrochloride]: ACCEPTABLE See DMF (b) (4)  
 Inspection:

DO Recommendation Withhold Firm not Ready (b) (4)

OC Recommendation Withhold DO Recommendation (b) (4)

S.3 Characterization[pseudoephedrine hydrochloride] ACCEPTABLE See DMF (b) (4).

S.4 Control of Drug Substance [pseudoephedrine hydrochloride, (b) (4)]

S.6 Container Closure System[pseudoephedrine hydrochloride]: ACCEPTABLE See DMF (b) (4).

S.7 Stability[pseudoephedrine hydrochloride]: ACCEPTABLE See DMF (b) (4).

S DRUG SUBSTANCE [guaifenesin, (b) (4)] ACCEPTABLE See Chem. Review #1

S DRUG SUBSTANCE [hydrocodone bitartrate, Mikart]

S DRUG SUBSTANCE [pseudoephedrine hydrochloride, Mikart]

S DRUG SUBSTANCE [guaifenesin, Mikart]

No information provided.

The applicant will need to provide information regarding the controls for each drug substance when tested by Mikart as part of the complete CMC information package.

P DRUG PRODUCT (b) (4)]

P.1 Description and Composition of the Drug Product [(b) (4)] ACCEPTABLE See Chem. Review #1

P.2 Pharmaceutical Development: [(b) (4)] ACCEPTABLE See Chem. Review #1

P.3. Manufacture [(b) (4)] ACCEPTABLE See Chem. Review #1

P.3.1 Manufacturers [(b) (4)]

Original

Site	Function	Inspection Status from EES		
		Status	Basis	Date
(b) (4)	Manufacturing and Testing	Recommend Withhold	No longer in operation	(b) (4)
	Alternative Testing Site	Acceptable	Based on Profile	

Chemistry Review #2 NDA 22279

(b) (4)	Alternative Testing Site	Not entered into EES		
	Alternative Testing Site	Acceptable	Based on Profile	(b) (4)

Not Acceptable

P.3.2 Batch Formula (b) (4) ] **ACCEPTABLE See Chem. Review #1**

P.3.3. Description of Manufacturing Process [ (b) (4) a] **ACCEPTABLE See Chem. Review #1**

P.3.4. Controls of Critical Steps and Intermediates [ (b) (4) ] **ACCEPTABLE See Chem. Review #1**

P.4 Control of Excipients (b) (4) **ACCEPTABLE See Chem. Review #1**

P.5 Control of Drug Product (b) (4) **ACCEPTABLE See Chem. Review #1**

P.6 Reference Standards or Materials (b) (4) **ACCEPTABLE See Chem. Review #1**

P.7 Container Closure System: (b) (4) **ACCEPTABLE See Chem. Review #1**

P.8 Stability (b) (4) **ACCEPTABLE See Chem. Review #1**

A APPENDICES N/A

R REGIONAL INFORMATION (b) (4)

R1 Executed Batch Records. (b) (4) **ACCEPTABLE See Chem. Review #1**

R2 Comparability Protocol N/A

R3 Methods Validation Package N/A

II. LABELING (b) (4) **ACCEPTABLE See Chem. Review #1**

**P DRUG PRODUCT [Mikart]** No information provided.

**A APPENDICES** N/A

**R REGIONAL INFORMATION [Mikart]**

**R1 Executed Batch Records. [Mikart] No information provided.**

The applicant will need to provide sample executed batch records for the manufacture of the drug product at Mikart as part of the complete CMC information package.

**R2 Comparability Protocol** N/A

**R3 Methods Validation Package** N/A

**II. LABELING [Mikart]** No information provided.

**III. DRAFT COMMENTS TO BE SENT TO APPLICANT:**

The NDA is approvable from the CMC perspective at this time. The quality information for the manufacturing site described in the application, (b) (4) cannot be used to support the quality of the drug product because, according to the amendment submitted on April 24, 2009, this site will not be used to manufacture drug product for the marketing of this drug. In order to approve the application, satisfactory quality information must be provided to the NDA for drug product manufactured at a new manufacturing site.

In addition all drug substance and drug product manufacturing sites must be in compliance with Current Good Manufacturing Practices.

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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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Arthur B. Shaw  
6/16/2009 03:41:21 PM  
CHEMIST

Ali Al-Hakim  
6/16/2009 04:22:00 PM  
CHEMIST

# **Chemistry Review Cover Sheet**

**NDA 22279**

**Hydrocodone Bitartrate,  
Pseudoephedrine Hydrochloride  
and Guaifenesin Oral Solution**

**Arthur B. Shaw, Ph.D.  
ONDQA/DPA1/DAARP**

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NDA 22279 Chemistry Review #1

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# Chemistry Review Data Sheet

1. NDA 22279
2. REVIEW #1
3. REVIEW DATE: April 27, 2009
4. REVIEWER: Arthur B. Shaw, Ph.D.
5. PREVIOUS DOCUMENTS: None
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>	<u>Comment</u>
Original	22-Aug-2008	None
Amendment	09-Oct-2008	Additional Response to Filing Letter
Amendment	12-Nov-2008	Response to Filing Letter
Amendment	01-Dec-2008	Updated stability data
Amendment	30-Mar-2009	Response to 19-Mar-2009
Amendment	21-Apr-2009	Change in sponsor to (b) (4)
Amendment	24-Apr-2009	Change in drug product manufacturing and testing sites

7. NAME & ADDRESS OF APPLICANT AND AGENT:

Applicant  
Name  
Address:



Agent  
Name

Mikart Inc.

Address:

1750 Chattahoochee Avenue  
Atlanta GA 30318

Agent

Lisa Apolis

Phone

404-351-4510

Fax

404-352-0351

E-mail

[lapolis@mikart.com](mailto:lapolis@mikart.com)

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Hydrocodone Bitartrate, Pseudoephedrine Hydrochloride and Guaifenesin Oral Solution
- b) Non-Proprietary Name (USAN): Hydrocodone Bitartrate, Pseudoephedrine Hydrochloride 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/decongestant/expectorant

11. DOSAGE FORM: Solution

12. STRENGTH/POTENCY: 2.5 mg hydrocodone bitartrate/30.0 mg pseudoephedrine hydrochloride/200 mg guaifenesin per 5 mL

13. ROUTE OF ADMINISTRATION: Oral

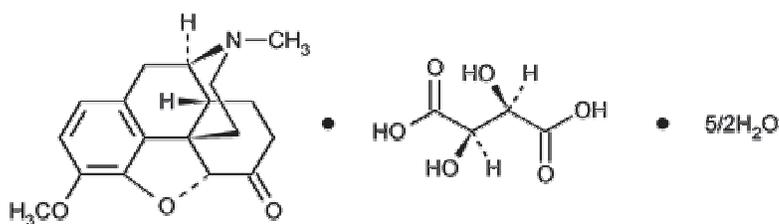
14. Rx/OTC DISPENSED:   X   Rx        OTC

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

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

A. Hydrocodone bitartrate

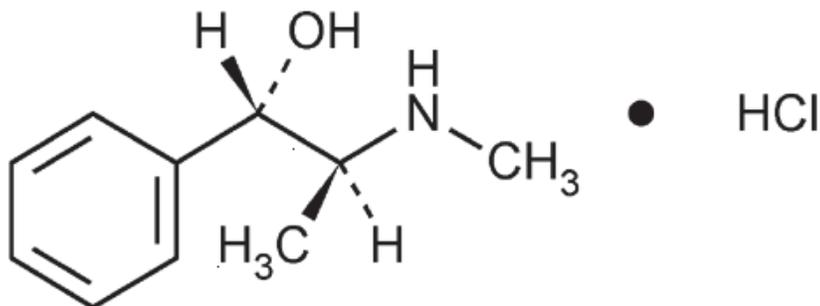
4,5 $\alpha$ -Epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5)



$C_{18}H_{21}NO_3 \cdot C_4H_6O_6$

494.490 (b) (4)

B. Pseudoephedrine HCl

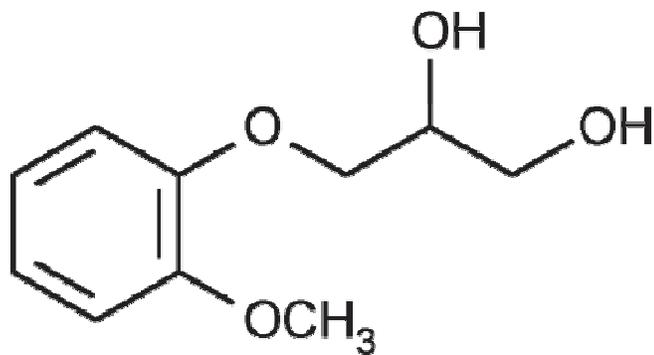


$C_{10}H_{15}NO \cdot HCl$

MW= 201.69

Benzenemethanol, -[1-(methylamino)ethyl]-, [S-(R\*,R\*)]-, hydrochloride

C. Guaifenesin



C<sub>10</sub>H<sub>14</sub>O<sub>4</sub>

198.22

1,2-Propanediol, 3-(2-methoxyphenoxy)-, (±)-.

## 17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**Reviewed: **ACCEPTABLE**

DMF	Holder	DMF Subject	Review Date
		(b) (4)	Not reviewed See below
			Adequate needs IR letter 04/27/2009
			Adequate 10/06/08 Yon de Lu Recent updates contain no significant new information.

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

DMF (b) (4) was found deficient in a review dated 03/10/2009. However the question of whether the issues involved in that review will prevent approval of an NDA supported by that DMF are still under discussion internally. Since the NDA itself is not approvable from a CMC point of view, resolution of those issues can wait for the applicant's complete response.

**B. Other Documents:**

IND (b) (4)

## 18. STATUS:

**CONSULTS/ CMC RELATED REVIEWS:**

Pharm/Tox consult for (b) (4) genotox studies in DMF (b) (4) Pending

EA waiver requested in 1.12.14. Granted **ACCEPTABLE**

Inspection: One drug substance manufacturing site (b) (4) for pseudoephedrine HCl) has an inspection assigned. The original drug product manufacturing, testing, and labeling site (b) (4) has closed and is not available for inspection. Mikart Laboratories has been identified as the new manufacturing and testing site for the drug product.

**The Chemistry Review for NDA 22279**

**I. Recommendations**

**1. Recommendation and Conclusion on Approvability**

The application is not approvable from a CMC point of view because the drug product manufacturing site identified in the original application ceased manufacturing early in 2008 and the new manufacturing site has just recently been named. The information provided for the original manufacturing site was satisfactory but there is no information about the manufacturing procedure or testing at the new site. One drug substance manufacturer has not been inspected yet.

**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), Pseudoephedrine HCl (PS) and Guaifenesin (GU) are USP items and their properties and synthesis have been assessed many times to support many applications. They are provided by three manufacturers, HC by (b) (4)

(b) (4) The DMFs have been recently reviewed and found acceptable except for the DMF for HC. There is still concern that the levels of (b) (4) may need to be controlled at a low level because this impurity is potentially genotoxic. The pharm/tox evaluation of the information provided by the DMF holder is still under review.

In addition the manufacturing site for the PS has not been inspected.

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

**2. Drug Product**

The drug product is an oral liquid so there is no issue regarding dissolution. The manufacturing process and controls as described for the original manufacturer (b) (4) are straightforward. All of the excipients are compendial except the colors, which are FD&C and D&C colors, and the flavoring, whose components are all GRAS. The specifications are adequate to control the drug product, including tests for all the drug substances and their impurities. The drug product is very stable, showing no changes in any of the tested parameters, including degradants, over the 12 months reporting period. Therefore an expiration period of 24 months is acceptable.

However since the NDA was recently sold to a new owner, (b) (4) and the new manufacturing and testing site, Mikart Inc. has just been identified. However there is no information about the manufacturing and testing at the new site.

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

The drug product is intended to be used for the symptomatic relief of cough (b) (4) nasal congestion (b) (4) and to (b) (4) loosen (b) (4) mucus (b) (4). Each of these drug substances has been approved separately for their labeled uses.

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

The drug is not approvable because, although the CMC review shows that the drug can be manufactured consistently at the original site (b) (4) to deliver the labeled amount of drug with each dose, there is no information about any CMC information at the new manufacturing site.

**III. Administrative**

See DFS signatures and cc's

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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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Arthur B. Shaw  
4/30/2009 04:39:02 PM  
CHEMIST

Ali Al-Hakim  
4/30/2009 06:39:43 PM  
CHEMIST

**OND Division of Pulmonary and Allergy Products**

**NDA: 22-279**

**Applicant:** (b) (4)

**Stamp Date:** 22-Aug-2008

**PDUFA Date:** 22-Jun-2009

**Proposed Proprietary Name: Not Chosen Yet**

**Established Name:** Hydrocodone bitartrate, Pseudoephedrine Hydrochloride, and Guaifenesin Oral Solution

**Dosage form and strength:** Oral Solution, 2.5 mg hydrocodone bitartrate, 30 mg pseudoephedrine hydrochloride, and 200 mg guaifenesin each, in 5 mL.

**Route of Administration:** Oral

**Indications:** Indicated for the symptomatic relief of cough, (b) (4) nasal congestion, and to (b) (4) loosen (b) (4) (mucus) (b) (4)

**Dose:** Adults (b) (4) Two teaspoonfuls (10 mL) every 4 hours, not to exceed 4 doses in 24 hours. (b) (4)

**PAL:** Prasad Peri, Ph.D. Branch 2/DPA I/ONDQA

**Fileability recommendation:** Acceptable for filing

**Review team recommendation:** Primary reviewer: Olen Stephens, Ph.D.

**Time goals:**

**Initial Quality Assessment in DFS:** by 10-Oct-2008 (NDA accessible on 27-Aug-2008)

**Chemistry filing memo in DFS:** by 10-Oct-2008 (after filing meeting)

Filing decision "Day 60": 6-Oct-2008

Filing Date "Day 74": 4-Nov-2008

**Chemistry Review (DR/IR) letter:** by 22-Jan-2009

Mid-cycle meeting "Month 5": 27-Jan-2009

**Final Chemistry Review "Month 8" in DFS:** by 22-Apr-2009

Wrap-Up Meeting (end of mo 8): April 22, 2009

Primary Review (1 wk after WU): April 29, 2009

Secondary Review (6 wks before Action): May 11, 2009

Labeling Tcon (5 wks before Action): May 12, 2009

CDTL Memo (4 wks before Action): May 25, 2009

Action Package Readiness: May 25, 2009

Division Director Memo: May 25, 2009

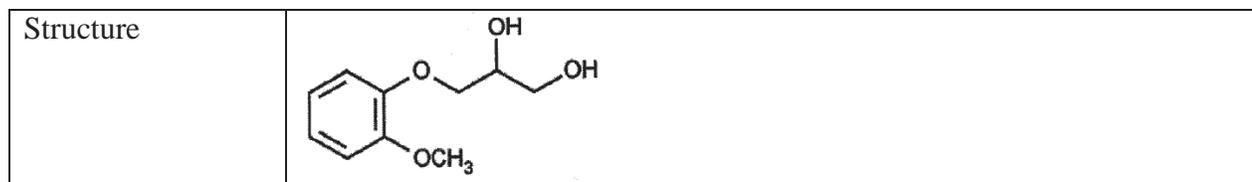
**PDUFA: 22-Jun-2009**

**Related Documents**

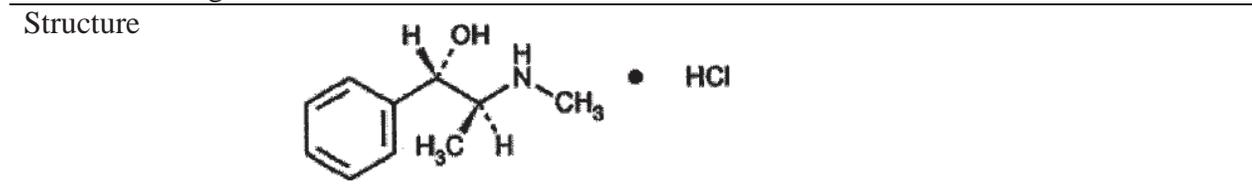
**INDs pertaining to this are:** 76,365

**NDAs pertaining to this are:** None

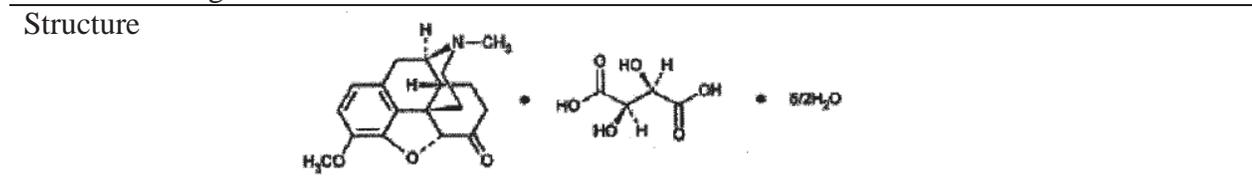
USAN/INN/JAN	<b>Guaifenesin USP</b>
Chemical Name	1,2-Propanediol, 3-(2-methoxyphenoxy) (b) (4)
CAS #	93-14-1
Molecular Formula	C <sub>10</sub> H <sub>14</sub> O <sub>4</sub>
Molecular weight	198.22
Melting Range	78°C-82°C



USAN/INN/JAN	<b>Pseudoephedrine Hydrochloride USP</b>
Chemical Name	Benzenemethanol, a-(1-(methylamino)ethyl)-, (S-(R*,R*))J, hydrochloride
CAS #	345-78-8
Molecular formula	$C_{10}H_{11}NO \cdot HCl$
Molecular weight	201.69



USAN/INN/JAN	<b>Hydrocodone Bitartrate USP</b>
Chemical Name	Morphinan-6-one, 4,5-epoxy-3-methoxy-17-methyl-, (5a)-, (R-(R*,R*))-2,3-dihydroxybutanedioate.(1 :1), hydrate (2:5); also known as 4,5a - Epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1 : 1) hydrate (2:5)
CAS #	(b) (4) 34195-34-1 (Hydrocodone Bitartrate)
Molecular formula	$C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2 \frac{1}{2} H_2O$
Molecular weight	494.490



CONSULTS/ CMC RELATED REVIEWS	COMMENT
<b>Clinical Pharm (BA/BE) - Dissolution</b>	No Applicable
<b>CDRH</b>	Not Applicable
<b>EA</b>	To be assessed by Primary Reviewer
<b>EES</b>	The drug substance site (b) (4) has an acceptable status however, it is not clear who does the stability testing of the drug substance. The drug product manufacturing sites are entered into EES on Sept. 5, 2007. No contact names and phone numbers are provided. They have been requested.
<b>DMETS/DDMAC</b>	Consensus is pending.
<b>Methods Validation</b>	Not necessary
<b>Microbiology</b>	Consult for antimicrobial assessment to be requested.
<b>Pharm/Tox</b>	Depends to stability data for leachables and impurities.
<b>Biometrics</b>	To be decided by the reviewer

### **Summary:**

- This is a standard (10 months) NDA in paper format with electronic labeling provided in SPL format. There is a Quality Overall Summary. This NDA is filed as a 505(b)2 application. This is a new combination containing three ingredients two of which (guaifenesin and pseudoephedrine) are listed in the OTC monograph part 341. Hydrocodone Bitartrate is a generally recognized antitussive, with efficacy established in DESI Notice #5213, dated June 1, 1982. Note that relevant NDAs for this application and that of Hycodan, Hycomine, and Tussionex. The NDA is based on a PK bioavailability study in a very few number (15-18) of patients. The three drug substances are specified as USP grade.
- This NDA is submitted by the applicant after the FDA issued a guidance called Marketed Unapproved Drugs—Compliance Policy Guide, which describes plans for enforcement in this area: "The FDA is telling manufacturers to either obtain approval for an unapproved drug or remove it from the market. Even if the drug has been marketed for many years with no known safety problems, companies will still need to comply. The absence of evidence of a safety problem does not mean a product is truly safe."

### **Drug Substance**

- The three drug substances are stated as USP grades and the proposed tests and certificates of analysis and specifications do support the compliance to the monograph.
- Hydrocodone bitartrate (b) (4)  
Hydrocodone is manufactured by (b) (4). The drug substance is referenced in a DMF (b) (4) which was found adequate for a solid oral dosage form in a review completed on April 19, 2007 by Rosario D'Costa, Ph.D. Special attention should be given to impurities in hydrocodone since several impurities have the potential to be genotoxic (b) (4). The agency (pharmacologist/toxicologists) has been alerting the manufacturers of hydrocodone of the potential genotoxic impurities and that they should limit the levels of these impurities to less than (b) (4) mcg/day. For the current indication the maximum daily dose of hydrocodone is 20 mg/day for Adults (b) (4).
- Pseudoephedrine hydrochloride USP is made by (b) (4). Information is presented in a DMF (b) (4). This DMF was evaluated for safety during the IND review process but has to be evaluated in detail for an NDA. (b) (4)
- Guaifenesin is obtained from (b) (4). The drug substance is referenced in a DMF (b) (4) and a letter of authorization is provided. The DMF was reviewed by G. Kang Ph.D. and found adequate for a solid, oral dosage form. Since that review, amendments were received with the following letter dates: 8/6/2007, 5/18/2006 and 4/24/2006. The two indicated 2006 amendments are administrative rather than technical. The 8/6/2007 amendment, based on the DMF holder's summary of changes made, and based upon summaries of stability data, does not present a safety concern.
- The formulation components and lot of drug product used for clinical trial and registration stability are reported in the table on the next page. The sponsor claims that the DMF holders have validated methods that are suitable for stability indication purposes and have documented stability data for the drug substance in the DMFs.

	Amount per 5 mL	Exhibit Batches	Proposed Commercial Batch
<b>Strength</b>	Hydrocodone Bitartrate 2.5 mg, Pseudoephedrine Hydrochloride 30 mg, and Guaifenesin 200 mg per 5 mL		
<b>Packaging Configuration</b>	(b) (4) white plastic HDPE (b) (4) bottle	(b) (4)	(b) (4) White Plastic
<b>Batch Size (kg)</b>	N/A	(b) (4)	(b) (4)
<b>Ingredient</b>	Ingredient (Amount/mL)	Ingredient Amount/Batch (b) (4)	Ingredient Amount/Batch
<b>Hydrocodone Bitartrate USP</b>	2.5 mg	(b) (4)	
<b>Pseudoephedrine Hydrochloride USP</b>	30 mg		
<b>Guaifenesin USP</b>	200 mg		
<b>Sorbitol (b) (4) USP</b>	(b) (4)		
<b>Glycerin USP</b>			
<b>Polyethylene Glycol (b) (4) USP</b>			
<b>Methylparaben NF</b>			
<b>Propylparaben NF</b>			
<b>Citric Acid (b) (4) USP</b>			
<b>Sodium Citrate (b) (4) USP</b>			
<b>Saccharin Sodium USP</b>			
<b>D&amp;C Red #33</b>			
<b>FD &amp; C Blue #1 (b) (4) Black</b>			
<b>Raspberry Flavor (b) (4)</b>			
<b>Purified Water USP</b>			

**Drug Product**

- Drug Product is an aqueous, (b) (4) flavored oral solution. It is a transparent liquid with a violet color that has a black raspberry (b) (4)
- Proposed commercial scale is stated to be (b) (4) L. Most excipients are USP or NF grade. D&C Red, FD&C Blue #1 are FDA certified colors. (b) (4) Black Raspberry Flavor (b) (4) (b) (4) has been provided in the NDA. Note that there was a discussion during the evaluation of safety during the IND safety review, and issues that need to be sorted out are stated below.
- Specifications for the colors need to be clarified in terms of their systematic names, (b) (4) D&C Red #33 but it is not clear what this really is. Similarly for FD&C Blue #1, (b) (4)
- Drug product is manufactured at (b) (4) The methods of manufacturing are relatively straight forward. (b) (4)

(b) (4)

Batch number	Batch size	Date of production	Use	Master formula number
L4917A	(b) (4)	12/10/07	Batch analysis and stability	(b) (4)
L4917	(b) (4)	12/04/07	Clinical trial	(b) (4)
M4922	(b) (4)	12/19/07	Batch analysis and stability	(b) (4)

- Drug product specifications are listed on the following page along with the results for three batches. Note that stability specifications use the same attributes.
- Stability data for three batches at accelerated and long term storage conditions are provided. For both the conditions, only 6 months of data are provided and the sponsor claims they have justified a 24 months shelf life. The reviewer needs to evaluate the proposed shelf life based on trending data and may ask for a biometrics consult to establish a shelf life. Note that ICH Q1A only allows a 12 months extrapolation if the data are robust. The sponsor does not mention any data on leachables.

**Stability testing of the submission batches (L4917A, L4917, M4922)**

Storage Conditions* (°C, % RH, light)	Container Closure System	Completed (and Proposed) Test Intervals
(b) (4)	(b) (4)	0, 1, 2, 3, 6
(b) (4)	(b) (4)	0, 3 6 (9,12,18,24) months

### CRITICAL ISSUES

- **Pharmaceutical development**

Formulation development has been reported and the selection of each excipient has been justified. The levels of monographed excipients are reported to be lower than the levels stated in the FDA's Inactive Ingredients Guide.

All ingredients are within the limits specified by the IIG.

Ingredients	Amount / unit	IIG Max
Sorbitol (b) (4) USP		(b) (4)
Glycerin USP		
Polyethylene Glycol (b) (4) USP		
Methylparaben NF		
Propylparaben NF		
Citric Acid (b) (4) USP		
Sodium Citrate (b) (4) USP		
Saccharin Sodium USP		

- **Dose Dumping.** Not applicable.

- **Microbial Testing:**

It is not clear if the sponsor has done a preservative effectiveness testing. The reviewer should evaluate the possibility of consulting microbiology staff if this is an issue. The proposed limits will need to be evaluated anyway by microbiology staff.

- **Overage in the formulation**

No overages are proposed for drug substance.

- **Excipients from Animal Origin.** None proposed.

- **OVI's in the drug Product.** Not applicable.

- **Manufacturing differences between pilot and commercial scales**

None proposed.

- **GMP status of the drug substance/drug product manufacturing sites.**

Note that the (b) (4) sites have been inspected for non-sterile dosage form (CSN) based on the Office of Compliance's web site. (b) (4) has never been inspected it appears. This will need inspection.

- **Safety of imprinting inks**

Although the sponsor claims no leachables, there are several extractables/leachables possible that will need to be evaluated in this NDA. The sponsor has not proposed acceptance criteria for leachables. The sponsor will need to justify the lack of testing for leachables.

- **Dissolution of the drug product**

Not applicable

- **Degradants in the drug product:**

So far the sponsor has not observed any significant degradation products as listed in the stability data.

- **Sensitivity of product to moisture and light.** This is an aq. solution packaged in HDPE bottles.

- **Weight Loss:** None proposed.

- **Shelf life** of the drug product proposed is 24 months. This will need to be evaluated.

- **Bulk Drug Product Stability Packaging Data and Protocol**

None proposed

- **Comparability Protocol:** None proposed.

- **Stability:** The first three consecutive commercial batches will be placed on stability. A stability commitment is provided.

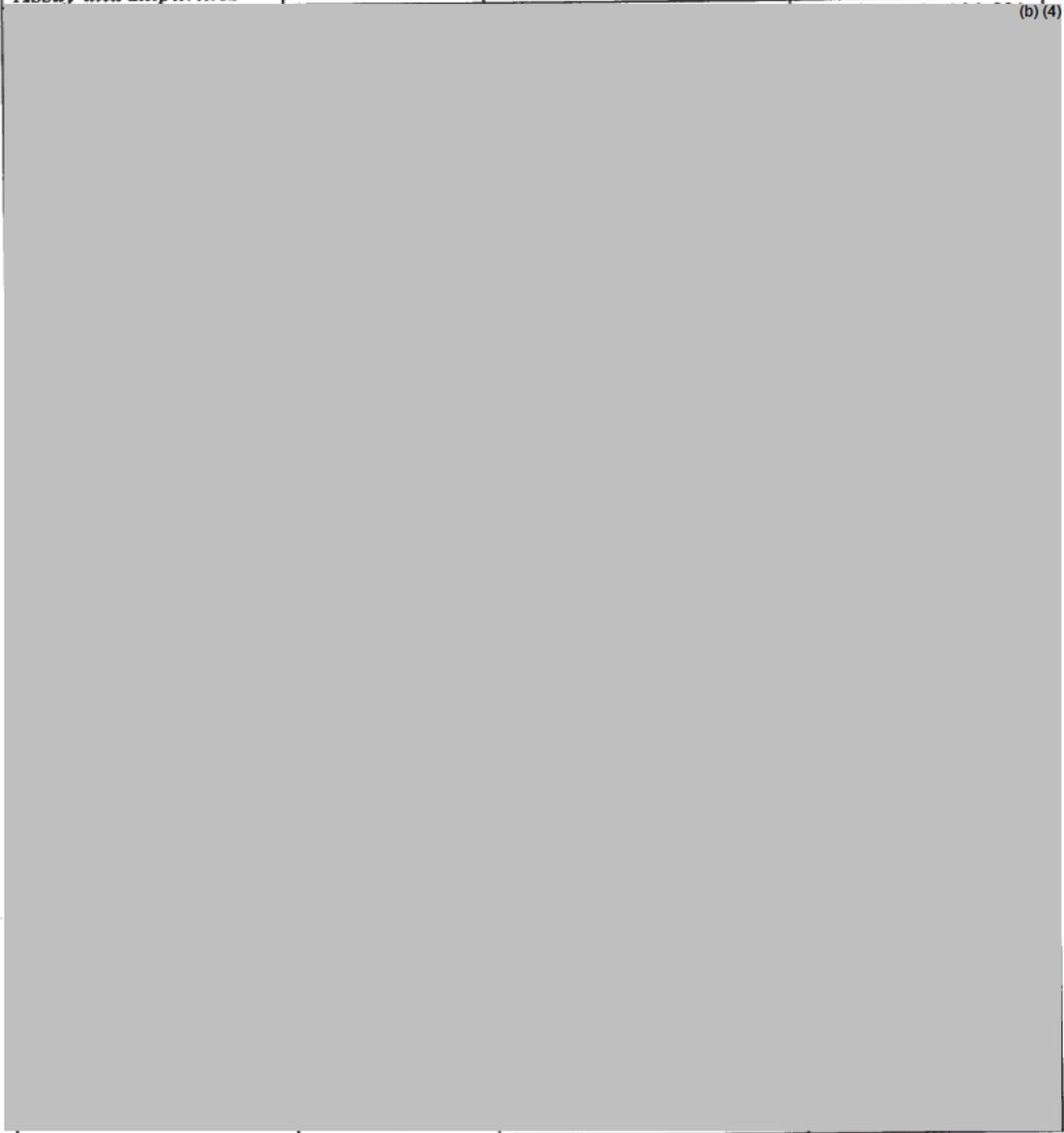
Drug product specifications with batch results are provided in the table below.

Test	Method	Limits	Submission Batch Results
Appearance	STP S34-A	(b) (4)	Lot L4917A: Pass Lot L4917: Pass Lot M4922: Pass
pH	SOP I-010		Lot L4917A: 3.4 Lot L4917: 3.4 Lot M4922: 3.5
Specific Gravity	STP S30-A		Lot L4917A: 1.1248 Lot L4917: 1.1248 Lot M4922: 1.1238
<i>Identification</i>	HPLC Retention Times		
- Hydrocodone Bitartrate 2½ Hydrate	STP S67A		Lot L4917A: Pass Lot L4917: Pass Lot M4922: Pass
- Pseudoephedrine Hydrochloride	STP S65A		Lot L4917A: Pass

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Prasad Peri, Ph.D., Division of Pre-Marketing Assessment 1, Branch 2

			Lot L4917: Pass Lot M4922: Pass
- Guaifenesin	STP S66A	Retention time meets standard	Lot L4917A: Pass Lot L4917: Pass Lot M4922: Pass
<i>Assay and Impurities</i>			

(b) (4)



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DMF	TYPE	HOLDER	ITEM REFERENCED	COMMENTS
(b) (4)	II			Reviewed by R. D.'Costa Ph.D. on 19-APR-2007 and found adequate. No review required.
	II			Reviewed by G. Kang, Ph.D. on 30-MAR-2006 and found adequate.
	II			DMF needs review.
	III			Needs review
	III			Needs review
	III			Needs review

• **CHEMISTRY NDA FILEABILITY CHECKLIST**

**IS THE CMC SECTION OF APPLICATION FILEABLE?    Yes**

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
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	To be provided, however all sites sent for EES and found acceptable based on profile.
6	Has an environmental assessment report or categorical exclusion been provided?		X	To be evaluated by reviewer.
7	Does the section contain controls for the drug substance?	X		Reference to DMFs and NDA
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	
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		
11	Have draft container labels been provided?	X		
12	Has the draft package insert been provided?	X		
13	Has an investigational formulations section been provided?		X	Described in the development report
14	Is there a Methods Validation package?	X		
15	Is a separate microbiological section included?	X		Antimicrobial Effectiveness Testing provided and will be evaluated
16	Is a production batch record provided	X		

**Draft CMC Comments for 74 day Letter**

- 1. Provide a statement to the NDA to indicate that all sites are ready for inspection at the time of the NDA submission.**
- 2. Provide references to indirect food additive regulations for all the packaging materials that are in contact with the formulation.**
- 3. We note that you have not provided us with an assessment of leachables in the drug product. Provide us results of your evaluation of extractables and leachables from the container closure system and how have you concluded that they do not exist and are not necessary for routine monitoring.**
- 4. We note that the proposed shelf life is 24 months even though you provided only 6 months of real time data. As per the ICHQ1A, a maximum of 12 months shelf life may be granted provided the stability data are robust.**
- 5. Pursuant to 21 CFR 25.31(a) or (b), provide an environmental assessment for the NDA demonstrating that the total concentration of each of the drug substances at the point of entry into the aquatic environment do not exceed 1 ppb.**
- 6. Provide a quantitative and qualitative chemical composition of the (b) (4) Black Raspberry Flavor (b) (4). Alternately this information may be provided in a authorized Drug Master File (DMF).**
- 7. Clarify if your drug product is packaged (b) (4) Provide the differences if any.**
- 8. Provide samples of the drug product in your proposed commercial packaging configuration.**
- 9. Provide draft mock ups (100 % size) of the proposed carton, container labels.**

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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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Prasad Peri  
10/6/2008 09:27:49 PM  
CHEMIST

Ali Al-Hakim  
10/7/2008 10:56:02 AM  
CHEMIST