

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**022439Orig1s000**

**CHEMISTRY REVIEW(S)**

NDA 22-439

**Zutripro**  
**(Hydrocodone Bitartrate, Chlorpheniramine Maleate and Pseudoephedrine Hydrochloride)**  
Oral Solution

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

**Applicant:** Cypress Pharmaceuticals, Inc.  
135 Industrial Blvd.,  
Madison, MS 39110

**Indication:**



**Presentation:** The drug product is an oral solution. Each 5 mL of solution contains 5.0 mg of hydrocodone bitartrate, 4 mg of chlorpheniramine maleate, and 60 mg of pseudoephedrine hydrochloride. The commercial Zutripro is packaged in a 16 fl. oz. white HDPE bottle; its professional sample is packaged in  bottle; both are closed with a white child resistant cap.

<b>EES Status:</b>	Recommendations:	Acceptable
<b>Consults:</b>	EA -	Categorical exclusion provided
	CDRH-	N/A
	Statistics -	N/A
	Methods Validation -	Not recommended
	Biopharm-	N/A
	Microbiology -	Acceptable
	Pharm/toxicology -	Acceptable

**Original Submission:** 06-November-2008  
**Re-submissions:** 08-December-2010  
**Post-Approval CMC Agreements:** None

### Background:

This is a resubmission of the NDA (6 months) in electronic 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 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:

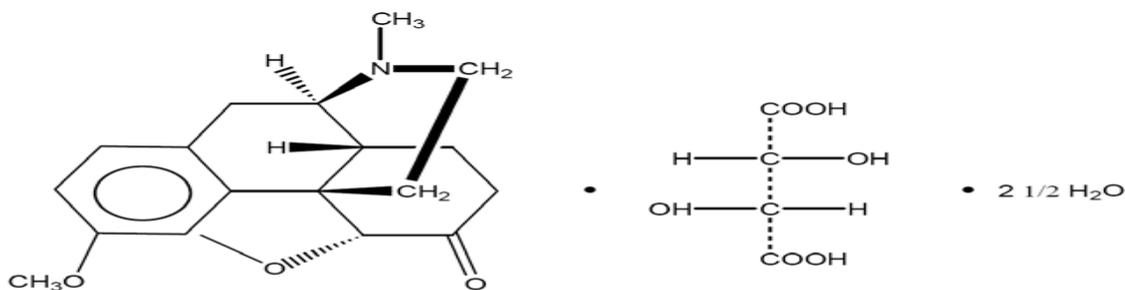
There are three drug substances for this NDA: hydrocodone bitartrate, chlorpheniramine maleate and pseudoephedrine hydrochloride. The three drug substances are stated as USP grades and the proposed tests and certificates of analysis and specifications do support the compliance to the monograph.

- **Hydrocodone bitartrate** USP is made by (b) (4) and referenced to DMF (b) (4). The DMF was reviewed and found acceptable (dated 12/14/2010).
- **Pseudoephedrine hydrochloride** USP is made by (b) (4). Information is presented in DMF (b) (4). This DMF was reviewed and found acceptable (review dated 8/3/2010)
- **Chlorpheniramine maleate** USP is obtained from (b) (4). The drug substance is referenced to DMF (b) (4). This DMF was reviewed on Mar 3, 2010 and found adequate..

Structures, molecular weight and molecular formulas are provided below.

### Hydrocodone bitartrate

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

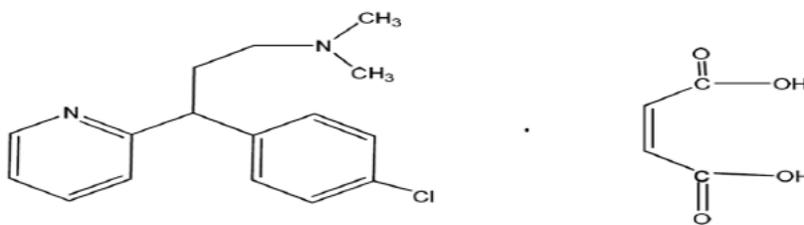


**Molecular Formula:**  $C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2\frac{1}{2}H_2O$

**Molecular Weight:** 494.490

### Chlorpheniramine maleate

**Chemical Name:** 2-Pyridinepropanamine,  $\gamma$ -(4-chlorophenyl)-N,N-dimethyl-(Z)-2-butenedioate (1:1)

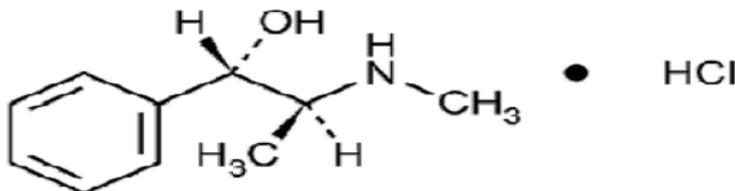


Molecular Formula:  $C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$

Molecular Weight: 390.86

### Pseudoephedrine hydrochloride

**Chemical Name:**  $\alpha$ -[1-(methylamino)ethyl]-[S-(R\*,R\*)] hydrochloride; (+)-Pseudoephedrine hydrochloride; Benzenemethanol and Dpseudoephedrine hydrochloride



Molecular Formula:  $C_{10}H_{15}NO \cdot HCl$

Molecular Weight: 201.69

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

### Drug Product:

The drug product is manufactured by (b) (4)

The methods of manufacturing are relatively straight forward. (b) (4)

Inactive excipients include water, citric acid, sodium citrate, sodium saccharine, sucrose, glycerin, propylene glycol, methylparaben, propylparaben and grape flavor. (b) (4)

(b) (4) The in process tests used are pH, appearance, density, and viscosity. The commercial

Zutripolis packaged in a 16 fl. oz. white HDPE bottle, its professional sample is packaged in <sup>(b) (4)</sup> bottle.

Drug product specifications include appearance, color, density, viscosity, deliverable volume, weight loss, identification, impurities, <sup>(b) (4)</sup> antimicrobial effectiveness test, microbial limit tests, total yeast and mold, <sup>(b) (4)</sup> and packaging.

Stability data provided for the drug product stored at 25°C, 24 months of expiry dating period is granted for the drug product.

**CMC issues that are still pending: None**

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

**Overall Conclusion:**

From a CMC perspective, the application is recommended for approval.

Prasad Peri, Ph.D.  
Chief, Branch VIII  
DPA III/ONDQA

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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  
05/18/2011  
Recommend Approval

# **NDA 22-439**

**Zutripro  
(Hydrocodone Bitartrate, Chlorpheniramine Maleate and  
Pseudoephedrine Hydrochloride)  
Oral Solution**

**Cypress Pharmaceuticals, Inc.**

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

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# Chemistry Review Data Sheet

1. NDA 22-439
2. REVIEW #: 4
3. REVIEW DATE: 12-Apr-2011
4. REVIEWER: Xiaobin Shen, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original	06-Nov-2008
Amendment 0001	26-Nov-2008
Amendment 0002	26-Jan-2009
Amendment 0003	28-Jan-2009
Amendment 0004	29-Jan-2009
Amendment 0005	04-Mar-2009
Amendment 0006	08-Apr-2009
Amendment 0007	19-May-2009
Amendment 0008	10-Jul-2009
Amendment 0009	10-Dec-2009
Amendment 0010 <sup>1</sup>	03-Feb-2010
Amendment 0011 <sup>1</sup>	17-Feb-2010
Amendment 0012	09-Apr-2010

<sup>1</sup>. Contains no CMC information.

6. SUBMISSION(S) BEING REVIEWED:

## Chemistry Review Data Sheet

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment 0013 (Safety information)	20-Apr-2010
Amendment 0014 (Proprietary name review withdrawal request)	27-Apr-2010
Amendment 0015 (New proprietary name review request)	30-Apr-2010
Amendment 0016 (Proposed plan for post- approval pediatric studies request)	06-May-2010
Amendment 0017 (Response to labeling deficiency comments)	17-May-2010
Amendment 0018 (Pediatric plan related responses)	19-May-2010
Amendment 0020 (Resubmission to 11-Jun-2011 CR Letter)	08-Dec-2010
Amendment 0021 (Request for proprietary name review)	10-Dec-2010
Amendment 0022 (Updates to 10-Dec-2010 submission)	28-Dec-2010
Amendment 0023 (Response to clinical information request)	08-Feb-2011

## 7. NAME &amp; ADDRESS OF APPLICANT:

Name: Cypress Pharmaceuticals, Inc.

Address: 135 Industrial Blvd., Madison, MS 39110

Representative: Robert L. Lewis II

Telephone: 1-800-856-4393 ext. 120

Facsimile: 601-853-1567

## Regulatory Agent Contact Information:

Address: Beckloff Associates, Inc.  
Commerce Plaza II, Suite 300  
7400 West 110<sup>th</sup> Street,  
Overland Park, KS 66210

Representative: William (Trey) Putnam

Telephone: 913-451-3955

Facsimile: 913-451-3846

All communications regarding this NDA are requested to be sent to the regulatory agent.

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

## Chemistry Review Data Sheet

- a) Proprietary Name: Zutripro;  
b) Non-Proprietary Name (USAN): Hydrocodone Bitartrate/Chlorpheniramine Maleate/Pseudoephedrine Hydrochloride  
c) Code Name/# (ONDC only): N/A  
d) Chem. Type/Submission Priority (ONDC 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 — Hycodan<sup>®</sup> Syrup, 5 mg/5 mL, NDA 005213, Endo Pharmaceuticals.

Chlorpheniramine Maleate — OTC monograph.

Pseudoephedrine Hydrochloride — OTC monograph.

## 10. PHARMACOL. CATEGORY:

Hydrocodone bitartrate is an antitussive (cough suppressing); Chlorpheniramine Maleate is an antihistamine; and pseudoephedrine hydrochloride is a nasal decongestant.

## 11. DOSAGE FORM: Oral Solution

## 12. STRENGTH/POTENCY: 5 mg Hydrocodone Bitartrate / 4 mg Chlorpheniramine Maleate / 60 mg Pseudoephedrine Hydrochloride 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

Not a SPOTS product

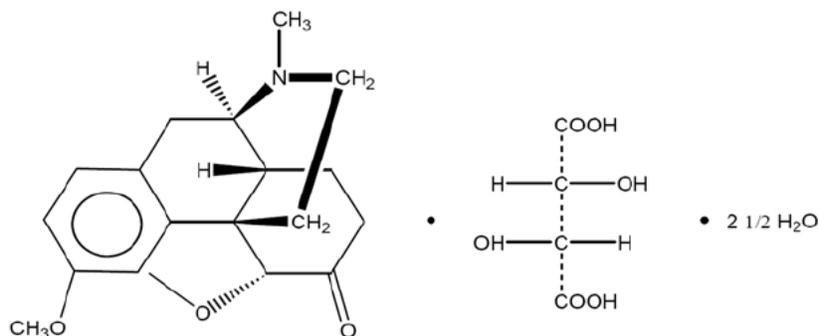
## Chemistry Review Data Sheet

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

There are three active pharmaceutical ingredients in this product.

Hydrocodone Bitartrate:

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

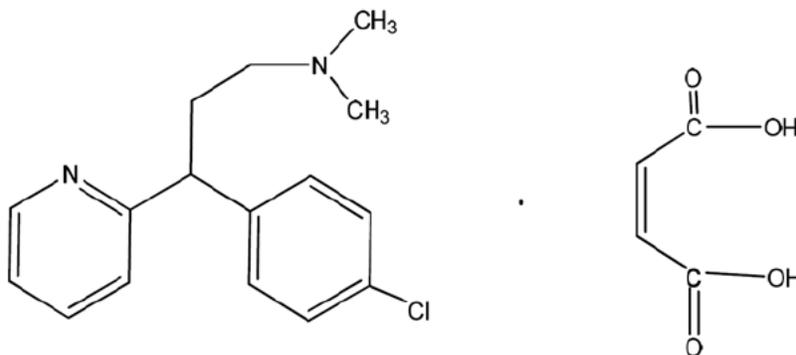


Molecular Formula:  $C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2\frac{1}{2}H_2O$

Molecular Weight: 494.490

Chlorpheniramine Maleate:

2-Pyridinepropanamine,  $\gamma$ -(4-chlorophenyl)-*N,N*-dimethyl-, (*Z*)-2-butenedioate (1:1)



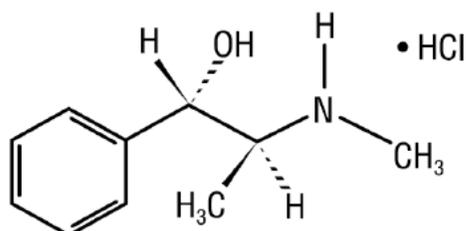
Molecular Formula:  $C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$

Molecular Weight: 390.86

Pseudoephedrine Hydrochloride:

[*S*-(*R*\*,*R*\*)]- $\alpha$ -[1-(methylamino)ethyl]-benzenemethanol hydrochloride

## Chemistry Review Data Sheet

Molecular Formula: C<sub>10</sub>H<sub>15</sub>NO·HCl

Molecular Weight: 201.69

**Comment:** The applicant provided chemical name is incorrect:  $\alpha$ -[1-(methylamino)ethyl]-[S-(R\*,R\*)] hydrochloride.

## 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)	3	Adequate	14-Dec-2010	The DMF is deemed adequate in support of an oral solution
	II			1	Adequate	03-Mar-2010	The DMF is deemed adequate in support of an oral solution
	II			3	Adequate	03-Aug-2010	The DMF is deemed adequate in support of an oral solution
	III			4			
	III			4			
	IV			1	Adequate	26-Mar-2010	The review deemed it adequate in support of an oral solution
	III			4			
	III			4			

Chemistry Review Data Sheet

		(b) (4)				
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<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
IND	102177	Oral solution, 5 mg Hydrocodone Bitartrate, 4 mg Chlorpheniramine Maleate, and 60 mg Pseudoephedrine Hydrochloride per 5 mL

18. STATUS:

**ONDQA:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA	NA	NA
EES	Adequate	23-Mar-2010	NA
Pharm/Tox	Adequate	23-Mar-2010	Grace Lee
Biopharm	NA	NA	NA
LNC	NA	NA	NA
Methods Validation	Validation is not required by FDA Lab	30-Jun-2009	Xiaobin Shen
DMEPA/OSE	NA	NA	NA
EA	Acceptable	30-Jun-2009	Xiaobin Shen
Microbiology	Acceptable	30-Jun-2009	James McVey

# The Chemistry Review for NDA 22-439

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls standpoint, an approval action is recommended for this NDA.

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

NA.

### II. Summary of Chemistry Assessments

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

The oral solution drug product is a clear, colorless to light-yellow solution with a grape odor. It is indicated for (b) (4)

Each 5 mL of the solution contains 5.0 mg of hydrocodone bitartrate, 4 mg of chlorpheniramine maleate, and 60 mg of pseudoephedrine hydrochloride. In addition to the three active pharmaceutical ingredients, it contains excipients commonly used in oral solution products (water, citric acid, sodium citrate, sodium saccharine, sucrose, glycerin, propylene glycol, methylparaben, propylparaben and grape flavor). The commercial product is packaged in a 16 fl. oz. white HDPE bottle, its professional sample is packaged in (b) (4) bottle.

The process used to manufacture the commercial product (b) (4) is equivalent to that used for the product used in the clinical studies (b) (4). The product is manufactured by (b) (4). Microbial limit testing is performed by (b) (4). Testing of raw materials is performed by (b) (4). cGMP status of all facilities are acceptable.

Up to 24 month stability data are provided. The data support the claimed 24 month expiry. The solution color at 24 month reached the stability specification (b) (4). Specified impurities (b) (4) have not been detected or remain below reporting limits in the drug product at the 24 month time point when stored at 25°C/60% RH. They will continue to be tested. The unspecified

## Chemistry Assessment Section

impurity at (b) (4) still within the (b) (4) limit.

There are three drug substances for this NDA: hydrocodone bitartrate, chlorpheniramine maleate, and pseudoephedrine hydrochloride.

1- Hydrocodone bitartrate (INN & USAN) was approved by FDA and marketed as Hycodan<sup>®</sup> Syrup since 1988. Hydrocodone is a semi synthetic narcotic antitussive and analgesic. Hydrocodone is a white or slightly yellow-white powder that is soluble in water and slightly soluble in alcohol. It is manufactured by (b) (4) and referenced to DMF (b) (4), which was last reviewed on 14-Dec-2010 by Dr. Maria Manzoni and found adequate. The EES status of the drug substance manufacturing facilities is acceptable. The drug product manufacturer's release specifications for hydrocodone bitartrate comply with the USP monograph and include appearance, identification, specific rotation, pH, loss on drying, residue on ignition, chloride, assay, related substances (specified and unspecified), residual solvents, and microbial limits. Hydrocodone bitartrate drug substance is packaged in (b) (4). The retest date is (b) (4) from the manufacturing date.

2- Chlorpheniramine maleate is an OTC monograph item. Chlorpheniramine is an antihistamine drug that prevents released histamine from dilating capillaries and causing edema of the respiratory mucosa. Chlorpheniramine maleate is a white crystalline powder that is freely soluble in water and alcohol. It is manufactured by (b) (4) and referenced to DMF (b) (4). This DMF was reviewed on May 27, 2009 and found inadequate. The (b) (4) in DMF (b) (4) was identified as a potential structural alert for genotoxicity, the DMF holder was notified on June 3, 2009 to reduce the level of (b) (4) to no more than (b) (4)/day or conduct a bacterial reverse assay to qualify the proposed specification. The DMF holder later qualified this impurity and the DMF became adequate on 03-Mar-2010. The EES status of the drug substance manufacturing facilities is acceptable. The drug product manufacturer's release specifications for chlorpheniramine maleate comply with the USP monograph and include appearance, identification, melting range, loss on drying, residue on ignition, assay, related substances (specified and unspecified), (b) (4). Chlorpheniramine maleate drug substance is packaged in (b) (4). The retest date is (b) (4) from the manufacturing date.

3- Pseudoephedrine hydrochloride is also an OTC monograph item. Pseudoephedrine hydrochloride is an orally active sympathomimetic amine and exerts a decongestant action on the nasal mucosa. Pseudoephedrine hydrochloride is a white to almost white crystalline powder that is freely soluble in water. It is manufactured by (b) (4) and referenced to DMF (b) (4). This DMF was last reviewed by Dr. Gil Jong Kang on 03-Aug-2010 and deemed adequate. The EES status of the drug substance manufacturing facilities is acceptable.

## Chemistry Assessment Section

The drug product manufacturer's release specifications for pseudoephedrine hydrochloride comply with the USP monograph and include appearance, identification, melting range, pH, specific rotation, loss on drying, residue on ignition, ordinary impurities, assay, related substances (specified and unspecified), (b) (4). Pseudoephedrine hydrochloride drug substance is packaged in (b) (4). The retest date is (b) (4) from the manufacturing date.

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

The drug product is an oral solution, each commercial package contains 16 fl. oz. and each professional sample contains (b) (4). Each 5 mL of the oral solution contains 5 mg of hydrocodone bitartrate, 4 mg of chlorpheniramine maleate, and 60 mg of pseudoephedrine hydrochloride.

Dosing for adults (b) (4) is 5 mL every 4 to 6 hours as needed but not to exceed 4 doses (20 mL) in 24 hours. (b) (4)

The manufacturer proposed a two year expiry with 20 C to 25 C storage condition, the firm provided 24 month real time stability data to support the two year expiry. The 24 month expiry is acceptable.

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

This is a 505b(2) application. From the perspective of chemistry, manufacturing and control, this drug product is recommended for approval.

The oral solution consists of three active moieties. The first active hydrocodone bitartrate was approved by FDA and marketed as Hycodan<sup>®</sup> Syrup since 1988. The other two actives chlorpheniramine maleate, and pseudoephedrine hydrochloride are both OTC monograph articles. All three drug substances have adequate controls (specifications) and stability characteristics.

The drug product excipients are all of USP/NF grade. All excipients in the drug product formulation are present at levels below the highest in US approved drug products. The container closure systems are typical for oral solutions and provided adequate information in the NDA. The drug product is very stable and the provided stability data support 24 month expiry.

EES (Establishment Evaluation System) status is acceptable for all manufacturing facilities.

The labeling and package insert are acceptable from CMC perspective.

**III. Administrative**

## Chemistry Assessment Section

**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**

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/s/  
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XIAOBIN SHEN

04/12/2011

The NDA is recommended for approval from CMC perspective.

PRASAD PERI

04/12/2011

I concur

# **NDA 22-439**

**(b) (4)**  
**(proposed Trade name)**  
**(Hydrocodone Bitartrate, Chlorpheniramine Maleate and**  
**Pseudoephedrine Hydrochloride)**  
**Oral Solution**

**Cypress Pharmaceuticals, Inc.**

**Xiaobin Shen, Ph.D.**

**Division of Pulmonary, Allergy and Rheumatology Drug**  
**Products**

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# Chemistry Review Data Sheet

1. NDA 22-439
2. REVIEW #: 3
3. REVIEW DATE: 21-Apr-2010
4. REVIEWER: Xiaobin Shen, Ph.D.

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original	11/06/2008
Amendment 0001	11/26/2008
Amendment 0002	01/26/2009
Amendment 0003	01/28/2009
Amendment 0004	01/29/2009
Amendment 0005	03/04/2009
Amendment 0006	04/08/2009
Amendment 0007	05/19/2009
Amendment 0008	07/10/2009

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment 0009	12/10/2009
Amendment 0010 <sup>1</sup>	02/03/2010
Amendment 0011 <sup>1</sup>	02/17/2010
Amendment 0012	04/09/2010

<sup>1</sup>. Contains no CMC information.

7. NAME & ADDRESS OF APPLICANT:

## Chemistry Review Data Sheet

Name: Cypress Pharmaceuticals, Inc.

Address: 135 Industrial Blvd., Madison, MS 39110

Representative: Robert L. Lewis II

Telephone: 1-800-856-4393 ext. 120

Facsimile: 601-853-1567

## Regulatory Agent Contact Information:

Address: Beckloff Associates, Inc.  
Commerce Plaza II, Suite 300  
7400 West 110<sup>th</sup> Street,  
Overland Park, KS 66210

Representative: William (Trey) Putnam

Telephone: 913-451-3955

Facsimile: 913-451-3846

All communications regarding this NDA are requested to be sent to the regulatory agent.

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

- a) Proprietary Name: (b) (4) Oral Solution (proposed);
- b) Non-Proprietary Name (USAN): Hydrocodone Bitartrate/Chlorpheniramine Maleate/Pseudoephedrine Hydrochloride
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC 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 — Hycodan<sup>®</sup> Syrup, 5 mg/5 mL, NDA 005213, Endo Pharmaceuticals.

Chlorpheniramine Maleate — OTC monograph.

Pseudoephedrine Hydrochloride — OTC monograph.

## Chemistry Review Data Sheet

## 10. PHARMACOL. CATEGORY:

Hydrocodone bitartrate is an antitussive (cough suppressing); Chlorpheniramine Maleate is an antihistamine; and pseudoephedrine hydrochloride is a nasal decongestant.

## 11. DOSAGE FORM: Oral Solution

12. STRENGTH/POTENCY: 5 mg Hydrocodone Bitartrate / 4 mg Chlorpheniramine Maleate / 60 mg Pseudoephedrine Hydrochloride 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

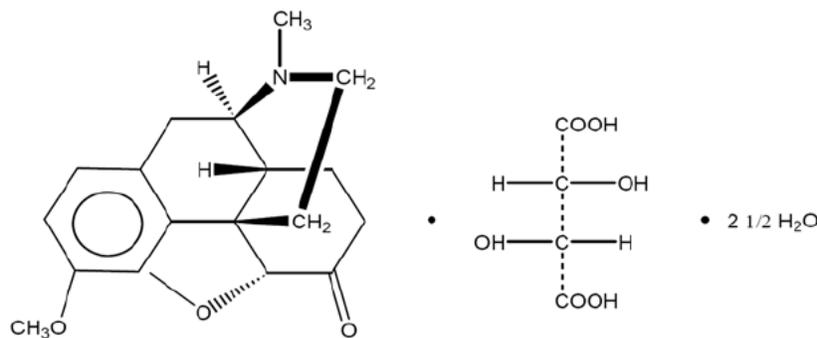
Not a SPOTS product

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

There are three active pharmaceutical ingredients in this product.

Hydrocodone Bitartrate:

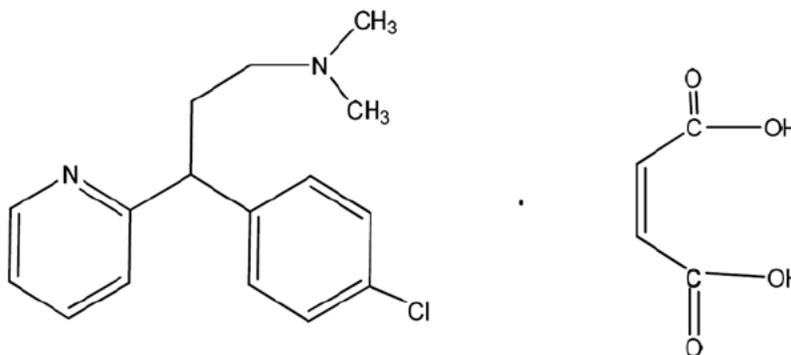
4,5 $\alpha$ -Epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5)



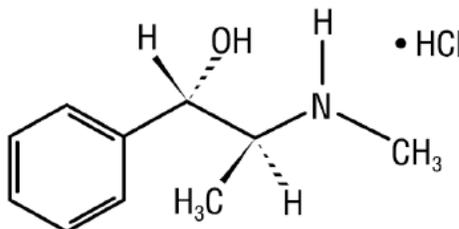
## Chemistry Review Data Sheet

Molecular Formula:  $C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2\frac{1}{2}H_2O$ 

Molecular Weight: 494.490

Chlorpheniramine Maleate:2-Pyridinepropanamine,  $\gamma$ -(4-chlorophenyl)-*N,N*-dimethyl-, (*Z*)-2-butenedioate (1:1)Molecular Formula:  $C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$ 

Molecular Weight: 390.86

Pseudoephedrine Hydrochloride:[*S*-(*R*\*,*R*\*)]- $\alpha$ -[1-(methylamino)ethyl]-benzenemethanol hydrochlorideMolecular Formula:  $C_{10}H_{15}NO \cdot HCl$ 

Molecular Weight: 201.69

**Comment:** The applicant provided chemical name is incorrect:  $\alpha$ -[1-(methylamino)ethyl]-[*S*-(*R*\*,*R*\*)] hydrochloride.

## 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)	3	Adequate	19-Feb-2010	The DMF is deemed adequate in support of an

Chemistry Review Data Sheet

(b) (4)		(b) (4)				oral solution
	II		1	Adequate	03-Mar-2010	The DMF is deemed adequate in support of an oral solution
	II		3	Adequate	15-Oct-2009	The DMF is deemed adequate in support of an oral solution
	III		4			
	III		4			
	IV		1	Adequate	26-Mar-2010	The review deemed it adequate in support of an oral solution
	III		4			
	III		4			

<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
IND	102177	Oral solution, 5 mg Hydrocodone Bitartrate, 4 mg Chlorpheniramine Maleate, and 60 mg Pseudoephedrine Hydrochloride per 5 mL

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	Adequate	23-Mar-2010	NA
Pharm/Tox	Adequate	23-Mar-2010	Grace Lee
Biopharm	NA	NA	NA
LNC	NA	NA	NA
Methods Validation	Validation is not required by FDA Lab	30-Jun-2009	Xiaobin Shen
DMEPA/OSE	NA	NA	NA
EA	Acceptable	30-Jun-2009	Xiaobin Shen
Microbiology	Acceptable	30-Jun-2009	James McVey

# The Chemistry Review for NDA 22-439

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls standpoint, an approval action is recommended for this NDA.

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

NA.

### II. Summary of Chemistry Assessments

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

The drug product (b)(4) (name not finalized) Solution is a clear, colorless to light-yellow solution with a grape odor. It is indicated for (b)(4)

Each 5 mL of the solution contains 5.0 mg of hydrocodone bitartrate, 4 mg of chlorpheniramine maleate, and 60 mg of pseudoephedrine hydrochloride. In addition to the three active pharmaceutical ingredients, (b)(4) contains excipients commonly used in oral solution products (water, citric acid, sodium citrate, sodium saccharine, sucrose, glycerin, propylene glycol, methylparaben, propylparaben and grape flavor). The commercial (b)(4) is packaged in a 16 fl. oz. white HDPE bottle, its professional sample is packaged in (b)(4) bottle.

The process used to manufacture the commercial product (b)(4) is equivalent to that used for the product used in the clinical studies (b)(4). The product is manufactured by (b)(4). Microbial limit testing is performed by (b)(4). Testing of raw materials is performed by (b)(4). cGMP status of all facilities are acceptable.

Specified impurities (b)(4) have not been detected or remain below reporting limits in the drug product at the 21 month time point when stored at 25 °C/60% RH. For this reason, the applicant removed these impurities from the specifications of the commercial batches. Instead, the applicant proposes to continue testing the registration batches for these impurities throughout the remainder of the 48 month stability program. If they detect the impurities during the extended

## Chemistry Assessment Section

stability at the proposed limits during the stability study, Cypress will evaluate the data and discuss plans with the Agency. The Agency does not agree with this approach and will send a comment to request the applicant to handle the change of specifications in a post-approval supplement.

Additionally, impurity (b) (4) was not detected in 6 month accelerated and 18 month 25 °C/60% RH stability data. It is removed from the commercial specifications. This is acceptable as (b) (4) is a drug substance process impurity and does not require to be reported in the drug product.

There are three drug substances for this NDA: hydrocodone bitartrate, chlorpheniramine maleate, and pseudoephedrine hydrochloride.

1- Hydrocodone bitartrate (INN & USAN) was approved by FDA and marketed as Hycodan<sup>®</sup> Syrup since 1988. Hydrocodone is a semi synthetic narcotic antitussive and analgesic. Hydrocodone is a white or slightly yellow-white powder that is soluble in water and slightly soluble in alcohol. It is manufactured by (b) (4) and referenced to DMF (b) (4), which was last reviewed on 19-Feb-2010 by Dr. Maria Manzoni and found adequate. The EES status of the drug substance manufacturing facilities is acceptable. The drug product manufacturer's release specifications for hydrocodone bitartrate comply with the USP monograph and include appearance, identification, specific rotation, pH, loss on drying, residue on ignition, chloride, ordinary impurities, organic volatile impurities, assay, related substances (specified and unspecified), residual solvents, and microbial limits. Hydrocodone bitartrate drug substance is packaged in (b) (4). The retest date is (b) (4) from the manufacturing date.

2- Chlorpheniramine maleate is an OTC monograph item. Chlorpheniramine is an antihistamine drug that prevents released histamine from dilating capillaries and causing edema of the respiratory mucosa. Chlorpheniramine maleate is a white crystalline powder that is freely soluble in water and alcohol. It is manufactured by (b) (4) and referenced to DMF (b) (4). This DMF was reviewed on May 27, 2009 and found inadequate. The (b) (4) in DMF (b) (4) was identified as a potential structural alert for genotoxicity, the DMF holder was notified on June 3, 2009 to reduce the level of (b) (4) to no more than (b) (4)/day or conduct a bacterial reverse assay to qualify the proposed specification. The DMF holder later qualified this impurity and the DMF became adequate on 03-Mar-2010. The EES status of the drug substance manufacturing facilities is acceptable. The drug product manufacturer's release specifications for chlorpheniramine maleate comply with the USP monograph and include appearance, identification, melting range, loss on drying, residue on ignition, assay, related substances (specified and unspecified), residual solvents, and microbial limits. Chlorpheniramine maleate drug substance is packaged in (b) (4). The retest date is (b) (4) from the manufacturing date.

## Chemistry Assessment Section

3- Pseudoephedrine hydrochloride is also an OTC monograph item. Pseudoephedrine hydrochloride is an orally active sympathomimetic amine and exerts a decongestant action on the nasal mucosa. Pseudoephedrine hydrochloride is a white to almost white crystalline powder that is freely soluble in water. It is manufactured by (b) (4) and referenced to DMF (b) (4). This DMF was last reviewed by Dr. Bahar Zarabi on 15-Oct-2009 and deemed adequate. The EES status of the drug substance manufacturing facilities is acceptable. The drug product manufacturer's release specifications for pseudoephedrine hydrochloride comply with the USP monograph and include appearance, identification, melting range, pH, specific rotation, loss on drying, residue on ignition, ordinary impurities, assay, related substances (specified and unspecified), organic volatile impurities, residual solvents, heavy metals and microbial limits. Pseudoephedrine hydrochloride drug substance is packaged in (b) (4). The retest date is (b) (4) from the manufacturing date.

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

The drug product (b) (4) is an oral solution, each commercial package contains 16 fl. oz. and each professional sample contains (b) (4). Each 5 mL of the oral solution contains 5 mg of hydrocodone bitartrate, 4 mg of chlorpheniramine maleate, and 60 mg of pseudoephedrine hydrochloride.

Dosing for adults (b) (4) is 5 mL every 4 to 6 hours as needed but not to exceed 4 doses (20 mL) in 24 hours. (b) (4)

(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. The 24 month expiry is acceptable.

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

This is a 505b(2) application. From the perspective of chemistry, manufacturing and control, this drug product is recommended for approval.

(b) (4) oral solution consists of three active moieties. The first active hydrocodone bitartrate was approved by FDA and marketed as Hycodan<sup>®</sup> Syrup since 1988. The other two actives chlorpheniramine maleate, and pseudoephedrine hydrochloride are both OTC monograph articles. All three drug substances have adequate controls (specifications) and stability characteristics.

The drug product excipients are all of USP/NF grade. The container closure systems are typical for oral solutions and provided adequate information in the NDA. The drug product is very stable and the provided stability data support 24 month expiry.

EES (Establishment Evaluation System) status is acceptable for all manufacturing facilities.

**Chemistry Assessment Section**

The product's trade name has been changed to (b) (4). The labeling and package insert are acceptable from CMC perspective.

**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**

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22439	ORIG-1	CYPRESS PHARMACEUTICA L INC	(b) (4) (HYDROCODONE BITARTRATE/CHLORPH

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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

04/21/2010

The NDA is recommended for approval. There are comments to be communicated to the applicant in the action letter.

PRASAD PERI

04/21/2010

I concur

**NDA 22-439**

(b) (4)

**(Hydrocodone Bitartrate, Chlorpheniramine Maleate and  
Pseudoephedrine Hydrochloride)  
Oral Solution**

**Cypress Pharmaceuticals, Inc.**

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

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# Chemistry Review Data Sheet

1. NDA 22-439
2. REVIEW #: 2
3. REVIEW DATE: 28-Aug-2009
4. REVIEWER: Xiaobin Shen, Ph.D.

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original	11/06/2008
Amendment 0001	11/26/2008
Amendment 0002	01/26/2009
Amendment 0003	01/28/2009
Amendment 0004	01/29/2009
Amendment 0005	03/04/2009
Amendment 0006	04/08/2009
Amendment 0007	05/19/2009

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment 0008	07/10/2009

7. NAME & ADDRESS OF APPLICANT:

Name: Cypress Pharmaceuticals, Inc.

## Chemistry Review Data Sheet

Address: 135 Industrial Blvd., Madison, MS 39110

Representative: Robert L. Lewis II

Telephone: 1-800-856-4393 ext. 120

Facsimile: 601-853-1567

## Regulatory Agent Contact Information:

Address: Beckloff Associates, Inc.  
Commerce Plaza II, Suite 300  
7400 West 110<sup>th</sup> Street,  
Overland Park, KS 66210

Representative: William (Trey) Putnam

Telephone: 913-451-3955

Facsimile: 913-451-3846

All communications regarding this NDA are requested to be sent to the regulatory agent.

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

- a) Proprietary Name: (b) (4) Oral Solution (proposed); It is later changed to (b) (4)
- b) Non-Proprietary Name (USAN): Hydrocodone Bitartrate/Chlorpheniramine Maleate/Pseudoephedrine Hydrochloride
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC 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 — Hycodan<sup>®</sup> Syrup, 5 mg/5 mL, NDA 005213, Endo Pharmaceuticals.

Chlorpheniramine Maleate — OTC monograph.

Pseudoephedrine Hydrochloride — OTC monograph.

## 10. PHARMACOL. CATEGORY:

## Chemistry Review Data Sheet

Hydrocodone bitartrate is antitussive (cough suppressing); Chlorpheniramine Maleate is antihistamine and pseudoephedrine hydrochloride a decongestant.

11. DOSAGE FORM: Oral Solution

12. STRENGTH/POTENCY: 5 mg Hydrocodone Bitartrate / 4 mg Chlorpheniramine Maleate / 60 mg Pseudoephedrine Hydrochloride 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

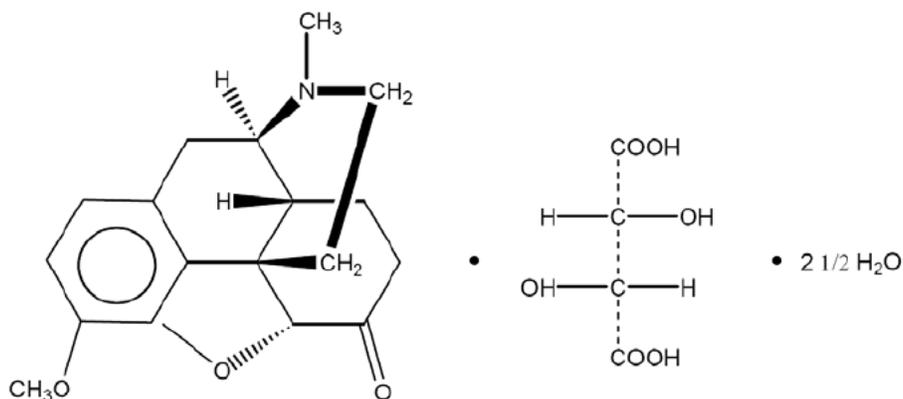
Not a SPOTS product

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

There are three active pharmaceutical ingredients in this product.

Hydrocodone Bitartrate:

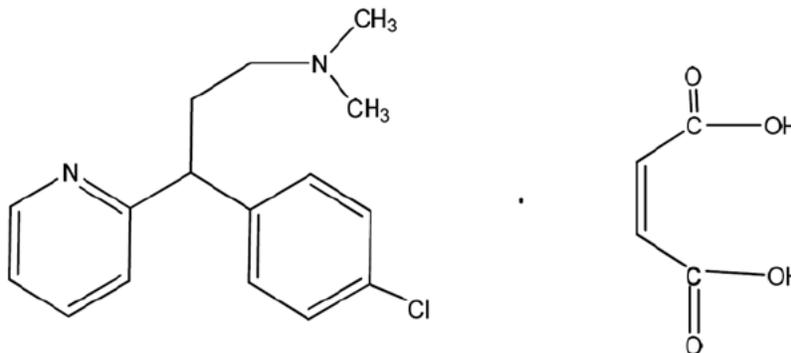
4,5 $\alpha$ -Epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5)



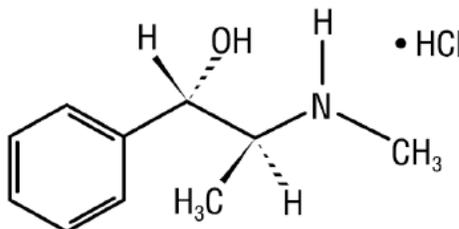
## Chemistry Review Data Sheet

Molecular Formula:  $C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2\frac{1}{2}H_2O$ 

Molecular Weight: 494.490

Chlorpheniramine Maleate:2-Pyridinepropanamine,  $\gamma$ -(4-chlorophenyl)-*N,N*-dimethyl-, (*Z*)-2-butenedioate (1:1)Molecular Formula:  $C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$ 

Molecular Weight: 390.86

Pseudoephedrine Hydrochloride:[*S*-(*R*\*,*R*\*)]- $\alpha$ -[1-(methylamino)ethyl]-benzenemethanol hydrochlorideMolecular Formula:  $C_{10}H_{15}NO \cdot HCl$ 

Molecular Weight: 201.69

**Comment:** The applicant provided chemical name is incorrect:  $\alpha$ -[1-(methylamino)ethyl]-[*S*-(*R*\*,*R*\*)] hydrochloride.

## 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)	3	Adequate	04-07-2009	The review in support of an oral solution identified

Chemistry Review Data Sheet

							deficiencies, which was corrected and then deemed adequate.
(b) (4)	II		(b) (4)	1	Inadequate	5-27-2009	(b) (4) was identified as a potential structural alert; DMF holder response is pending.
	II			3	Adequate	08-13-2008	Based on this and the previous reviews, the DMF is deemed adequate in support of an oral solution
	III			NA	NA	NA	NA
	III			NA	NA	NA	NA
	IV			3	Adequate	08-14-2008	The review deemed it adequate in support of an oral solution
	III			NA	NA	NA	NA
	III			NA	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
IND	102177	IND review summary indicated CMC related items are considered and evaluated in this NDA review.

18. STATUS:

**ONDQA:**

<b>CONSULTS/ CMC RELATED REVIEWS</b>	<b>RECOMMENDATION</b>	<b>DATE</b>	<b>REVIEWER</b>
Biometrics	NA	NA	NA
EES	Pending	8/28/2009	Marisa Stock
Pharm/Tox	Adequate	5/22/2009	Marcus Delatte
Biopharm	NA	NA	NA
LNC	Acceptable	3/30/2009	Felicia Duffy
Methods Validation	Validation is not required by FDA Lab	6/30/2009	Xiaobin Shen
OPDRA	NA	NA	NA
EA	Acceptable	3/30/2009	Xiaobin Shen
Microbiology	Acceptable	3/30/2009	James McVey

# The Chemistry Review for NDA 22-439

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls standpoint, the NDA is approvable pending adequate responses to the outstanding issues summarized at end of this review and acceptable cGMP recommendation from office of compliance.

#### B. 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)

The drug product (b) (4) is a clear, colorless to light-yellow oral solution with a grape odor. It is indicated for (b) (4)

Each 5 mL of the solution contains 5.0 mg of hydrocodone bitartrate, 4 mg of chlorpheniramine maleate, and 60 mg of pseudoephedrine hydrochloride. In addition to the three active pharmaceutical ingredients, (b) (4) contains excipients commonly used in oral solution products (e.g. water, citric acid, sodium citrate, sodium saccharine, sucrose, glycerin, propylene glycol, methylparaben, propylparaben and grape flavor). The commercial (b) (4) is packaged in a 16 fl. oz. white HDPE bottle, its professional sample is packaged in (b) (4) bottle.

The process used to manufacture the commercial product (b) (4) is equivalent to that used for the product used in the clinical studies (b) (4).

There are three drug substances for this NDA: hydrocodone bitartrate, chlorpheniramine maleate and pseudoephedrine hydrochloride.

1- Hydrocodone bitartrate (INN & USAN) was approved by FDA and marketed as Hycodan<sup>®</sup> Syrup since 1988. Hydrocodone is a semi synthetic narcotic antitussive and analgesic. Hydrocodone is a white or slightly yellow-white powder that is soluble in water and slightly soluble in alcohol. It is manufactured by (b) (4) and referenced to DMF (b) (4), which was last reviewed in April, 2009 by Dr. Maria Manzoni and found adequate. The DMF's EES status is acceptable. The drug

## Chemistry Assessment Section

product manufacturer release specifications for hydrocodone bitartrate comply with the USP monograph and include appearance, identification, specific rotation, pH, loss on drying, residue on ignition, chloride, ordinary impurities, organic volatile impurities, assay, related substances (specified and unspecified), (b) (4)

2- Chlorpheniramine maleate is an OTC monograph item. Chlorpheniramine is an antihistamine drug that prevents released histamine from dilating capillaries and causing edema of the respiratory mucosa. Chlorpheniramine maleate is a white crystalline powder that is freely soluble in water and alcohol. It is manufactured by (b) (4) and referenced to DMF (b) (4). This DMF was reviewed on May 27, 2009 and found inadequate. The (b) (4) in DMF (b) (4) is a potential structural alert for genotoxicity, the DMF holder was notified on June 3, 2009 to reduce the level of (b) (4) to no more than (b) (4)/day or conduct a bacterial reverse assay to qualify the proposed specification. The DMF's GMP site inspection was complete. The inspector identified two findings remain to be addressed and a recommendation on EES status is pending. The drug product manufacturer release specifications for chlorpheniramine maleate comply with the USP monograph and include appearance, identification, melting range, loss on drying, residue on ignition, assay, related substances (specified and unspecified), residual solvents, and microbial limits.

3- Pseudoephedrine hydrochloride is also OTC monograph item. Pseudoephedrine hydrochloride is an orally active sympathomimetic amine and exerts a decongestant action on the nasal mucosa. Pseudoephedrine hydrochloride is a white to almost white crystalline powder that is freely soluble in water. It is manufactured by (b) (4) and referenced to DMF (b) (4). This DMF was reviewed by Guoping Sun, Ph.D. in Feb. 2008 and deemed adequate. Arthur Shaw, Ph.D. reviewed it last in Aug. 2008 after the DMF was resubmitted in CTD-Q format and also deemed it adequate. The holder's EES status is acceptable. The drug product manufacturer release specifications for pseudoephedrine hydrochloride comply with the USP monograph and include appearance, identification, melting range, pH, specific rotation, loss on drying, residue on ignition, ordinary impurities, assay, related substances (specified and unspecified), organic volatile impurities, residual solvents, heavy metals and microbial limits.

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

The drug product (b) (4) is an oral solution, each commercial package contains 16 fl. oz. and each professional sample contains (b) (4). Each 5 mL of the oral solution contains 5 mg of hydrocodone bitartrate, 4 mg of chlorpheniramine maleate, and 60 mg of pseudoephedrine hydrochloride.

Dosing for adults (b) (4) is 5 mL every 4 to 6 hours as needed but not to exceed 4 doses (20 mL) in 24 hours. (b) (4)

The manufacturer proposed a two year expiry with 20 C to 25 C

## Chemistry Assessment Section

storage condition, the firm provided 12 month real time stability data to support the two year expiry and it is found acceptable.

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

From the perspective of chemistry, manufacturing and control, this drug product is approvable pending satisfactory responses to the outstanding CMC deficiencies and acceptable cGMP recommendation from office of compliance.

(b) (4) oral solution consists of three active moieties. The first active hydrocodone bitartrate was approved by FDA and marketed as Hycodan<sup>®</sup> Syrup since 1988. The other two actives chlorpheniramine maleate and pseudoephedrine hydrochloride are both OTC monograph articles.

There are CMC requests related to the all three drug substances and the drug product which need to be addressed by the DMF holders or the sponsors (see section III of the review summary in chemistry review No. 1). EES status are acceptable for all facilities except that for (b) (4). This site was inspected and currently pending on inspection recommendation.

The product's trade name has been changed to (b) (4) and deemed acceptable.

The labeling and package insert are acceptable from CMC perspective with minor comments.

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

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

**B. Endorsement Block**

ChemistName/Date: Xiaobin Shen/28-Aug-2009

ChemistryTeamLeaderName/Date:

ProjectManagerName/Date:

**C. CC Block**

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Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
----- NDA 22439	----- ORIG 1	----- CYPRESS PHARMACEUTICA L INC	----- (b) (4) (HYDROCODONE BITARTRATE/CHLORPH

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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

08/31/2009

This NDA is approvable pending satisfactory responses to CMC deficiencies including DMF, inspection and analytical methods and specifications.

ALI H AL HAKIM

08/31/2009

# NDA 22-439

(b) (4)

## (Hydrocodone Bitartrate, Chlorpheniramine Maleate and Pseudoephedrine Hydrochloride) Oral Solution

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

**Applicant:** Cypress Pharmaceuticals, Inc.  
135 Industrial Blvd.,  
Madison, MS 39110

**Indication:**

(b) (4)

**Presentation:** The drug product is an oral solution. Each 5 mL of solution contains 5.0 mg of hydrocodone bitartrate, 4 mg of chlorpheniramine maleate, and 60 mg of pseudoephedrine hydrochloride. The commercial (b) (4) is packaged in a 16 fl. oz. white HDPE bottle; its professional sample is packaged in (b) (4) bottle; both are closed with a white child resistant cap.

<b>EES Status:</b>	Recommendations:	Acceptable
<b>Consults:</b>	EA -	Categorical exclusion provided
	CDRH-	N/A
	Statistics -	N/A
	Methods Validation -	Not recommended
	Biopharm-	N/A
	Microbiology -	Acceptable
	Pharm/toxicology -	Acceptable

**Original Submission:** 07-November-2008  
**Re-submissions:** N/A  
**Post-Approval CMC Agreements:** None

## Background:

This is a standard (10 months) NDA in electronic 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 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:

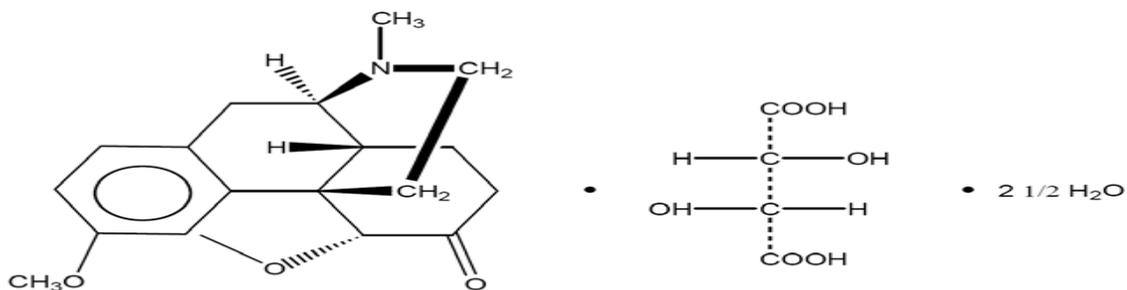
There are three drug substances for this NDA: hydrocodone bitartrate, chlorpheniramine maleate and pseudoephedrine hydrochloride. The three drug substances are stated as USP grades and the proposed tests and certificates of analysis and specifications do support the compliance to the monograph.

- **Hydrocodone bitartrate** USP is referenced to DMF (b)(4). The DMF was reviewed and found acceptable (review dated 04/07/2009).
- **Pseudoephedrine hydrochloride** USP is made by (b)(4). Information is presented in DMF (b)(4). This DMF was reviewed and found acceptable (review dated 8/13/2008)
- **Chlorpheniramine maleate** USP is obtained from (b)(4). The drug substance is referenced to DMF (b)(4). This DMF was reviewed on May 27, 2009 and found inadequate. The (b)(4) in DMF (b)(4) is a potential structural alert for geotoxicity, the DMF holder was notified on June 3, 2009 to reduce the level of (b)(4) to no more than (b)(4) /day or conduct a bacterial reverse assay to qualify the proposed specification. The DMF's EES status is pending.

Structures, molecular weight and molecular formulas are provided below.

### Hydrocodone bitartrate

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

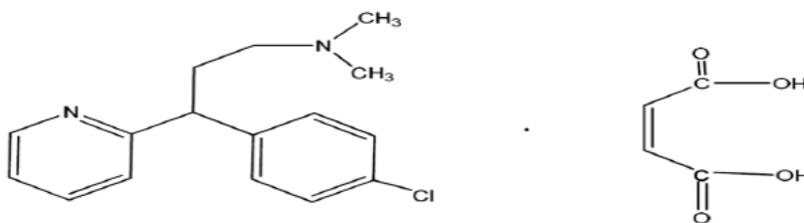


**Molecular Formula:**  $C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2\frac{1}{2}H_2O$

**Molecular Weight:** 494.490

### Chlorpheniramine maleate

**Chemical Name:** 2-Pyridinepropanamine,  $\gamma$ -(4-chlorophenyl)-N,N-dimethyl-(Z)-2-butenedioate (1:1)

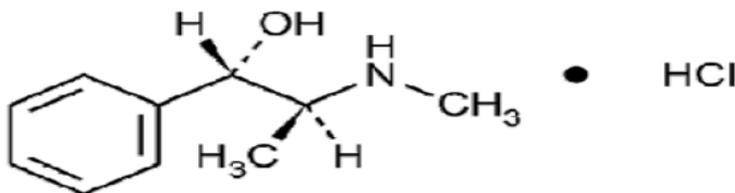


Molecular Formula:  $C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$

Molecular Weight: 390.86

### Pseudoephedrine hydrochloride

**Chemical Name:**  $\alpha$ -[1-(methylamino)ethyl]-[S-(R\*,R\*)] hydrochloride; (+)-Pseudoephedrine hydrochloride; Benzenemethanol and Dpseudoephedrine hydrochloride



Molecular Formula:  $C_{10}H_{15}NO \cdot HCl$

Molecular Weight: 201.69

**Conclusion:** The drug substance is not satisfactory.

### Drug Product:

Drug product is manufactured at by [REDACTED] (b) (4)

The methods of manufacturing are relatively straight forward. [REDACTED] (b) (4)

[REDACTED] Inactive excipients include water, citric acid, sodium citrate, sodium saccharine, sucrose, glycerin, propylene glycol, methylparaben, propylparaben and grape flavor. [REDACTED] (b) (4)

[REDACTED] (b) (4) The in process tests used are pH, appearance, density, and viscosity. The commercial

(b) (4) is packaged in a 16 fl. oz. white HDPE bottle, its professional sample is packaged in (b) (4) bottle. Drug product specifications include Appearance, color, density, viscosity, deliverable volume, weight loss, identification, impurities, (b) (4) antimicrobial effectiveness test, microbial limit tests, total yeast and mold, (b) (4) and packaging.

Based on the 12 months real time stability data provided for the drug product stored at 25°C, 24 months of expiry dating is granted for the drug product.

#### **CMC issues that are still pending**

There are many and significant outstanding CMC issues that are still pending for this NDA. The details of these deficiencies which were identified by the reviewer in chemistry review no. 1 dated July 08, 2009, were forwarded to the sponsor and we are currently awaiting the appropriate responses.

The main CMC deficiencies are related, but not limited, to

- DMF (b) (4) Deficiencies for hydrocodone bitartrate drug substance (impurities and related specifications)
- Test data for stability and microbial testing (b) (4)
- Establishing specifications for the potential degradants in drug product
- Reducing the total impurity level of the drug product
- Submission of additional stability data for drug product
- Reporting the related substances results of Hydrocodone Bitartrate, USP should be based on ICH guideline Q3A
- The specifications for total impurity acceptance criteria should be based on actual data from the long term stability study.

**Conclusion:** The drug product is not satisfactory.

#### **Overall Conclusion:**

From a CMC perspective, the application is approvable pending satisfactory responses to the CMC deficiencies.

Ali Al-Hakim, Ph.D.  
Branch Chief,  
DPA I/ONDQA

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this page is the manifestation of the electronic signature.**  
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/s/

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Ali Al-Hakim  
7/14/2009 10:42:20 AM  
CHEMIST

**NDA 22-439**

(b) (4)

**(Hydrocodone Bitartrate, Chlorpheniramine Maleate and  
Pseudoephedrine Hydrochloride)  
Oral Solution**

**Cypress Pharmaceuticals, Inc.**

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

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# Chemistry Review Data Sheet

1. NDA 22-439
2. REVIEW #: 1
3. REVIEW DATE: 07/08/2009
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

Amendment 0003

Amendment 0004

Amendment 0005

Amendment 0006

Amendment 0007

Document Date

11/06/2008

11/26/2008

01/26/2009

01/28/2009

01/29/2009

03/04/2009

04/08/2009

05/19/2009

## Chemistry Review Data Sheet

## 7. NAME &amp; ADDRESS OF APPLICANT:

Name: Cypress Pharmaceuticals, Inc.  
Address: 135 Industrial Blvd., Madison, MS 39110  
Representative: Robert L. Lewis II  
Telephone: 1-800-856-4393 ext. 120  
Facsimile: 601-853-1567

## Regulatory Agent Contact Information:

Address: Beckloff Associates, Inc.  
Commerce Plaza II, Suite 300  
7400 West 110<sup>th</sup> Street,  
Overland Park, KS 66210  
Representative: William (Trey) Putnam  
Telephone: 913-451-3955  
Facsimile: 913-451-3846

All communications regarding this NDA are requested to be sent to the regulatory agent.

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

- a) Proprietary Name: (b) (4) Oral Solution (proposed); It is later changed to (b) (4)  
b) Non-Proprietary Name (USAN): Hydrocodone Bitartrate/Chlorpheniramine Maleate/Pseudoephedrine Hydrochloride  
c) Code Name/# (ONDC only): N/A  
d) Chem. Type/Submission Priority (ONDC 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 — Hycodan<sup>®</sup> Syrup, 5 mg/5 mL, NDA 005213, Endo Pharmaceuticals.

Chlorpheniramine Maleate — OTC monograph.

## Chemistry Review Data Sheet

Pseudoephedrine Hydrochloride — OTC monograph.

**10. PHARMACOL. CATEGORY:**

Hydrocodone bitartrate is antitussive (cough suppressing); Chlorpheniramine Maleate is antihistamine and pseudoephedrine hydrochloride a decongestant.

**11. DOSAGE FORM:** Oral Solution

**12. STRENGTH/POTENCY:** 5 mg Hydrocodone Bitartrate / 4 mg Chlorpheniramine Maleate / 60 mg Pseudoephedrine Hydrochloride per 5 mL.

**13. ROUTE OF ADMINISTRATION:** Oral

**14. Rx/OTC DISPENSED:**      X   Rx           OTC

**15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)**

   SPOTS product – Form Completed

  X   Not a SPOTS product

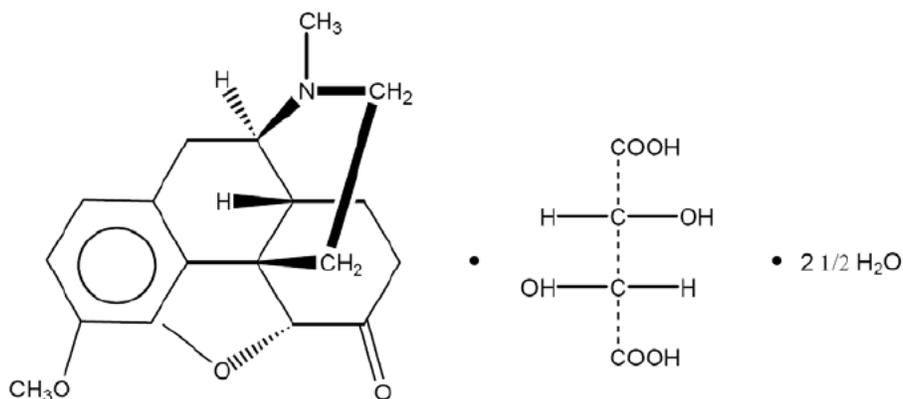
**16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:**

There are three active pharmaceutical ingredients in this product.

Hydrocodone Bitartrate:

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

## Chemistry Review Data Sheet

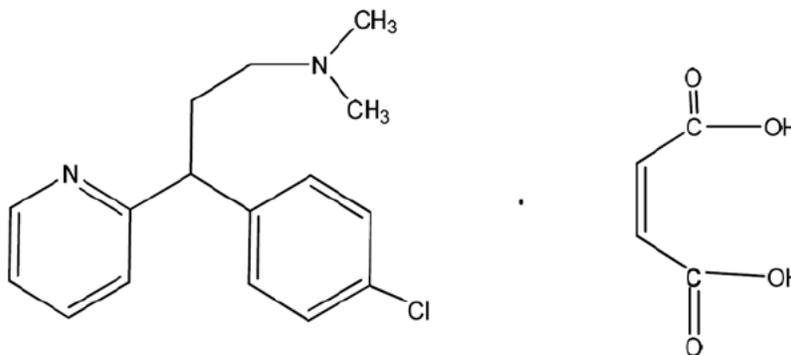


Molecular Formula:  $C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2\frac{1}{2}H_2O$

Molecular Weight: 494.490

Chlorpheniramine Maleate:

2-Pyridinepropanamine,  $\gamma$ -(4-chlorophenyl)-*N,N*-dimethyl-, (*Z*)-2-butenedioate (1:1)

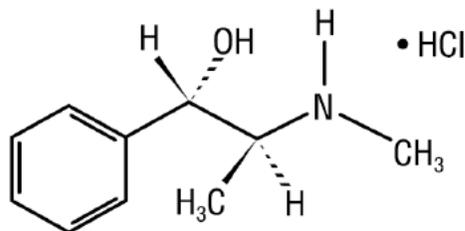


Molecular Formula:  $C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$

Molecular Weight: 390.86

Pseudoephedrine Hydrochloride:

[*S*-(*R*\*,*R*\*)]- $\alpha$ -[1-(methylamino)ethyl]-benzenemethanol hydrochloride



Molecular Formula:  $C_{10}H_{15}NO \cdot HCl$

Molecular Weight: 201.69

Chemistry Review Data Sheet

**Comment:** The applicant provided chemical name is incorrect:  $\alpha$ -[1-(methylamino)ethyl]-[S-(R\*,R\*)] hydrochloride.

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	04-07-2009	The review in support of an oral solution identified deficiencies, which was corrected and then deemed adequate.
	II		1	Inadequate	5-27-2009	(b) (4) was identified as a potential structural alert; DMF holder response is pending.	
	II		3	Adequate	08-13-2008	Based on this and the previous reviews, the DMF is deemed adequate in support of an oral solution	
	III		NA	NA	NA	NA	
	III		NA	NA	NA	NA	
	IV		3	Adequate	08-14-2008	The review deemed it adequate in support of an oral solution	
	III		NA	NA	NA	NA	
	III		NA	NA	NA	NA	

Chemistry Review Data Sheet

<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
IND	102177	IND review summary indicated CMC related items are considered and evaluated in this NDA review.

18. STATUS:

**ONDQA:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA	NA	NA
EES	Pending	6/30/2009	NA
Pharm/Tox	Adequate	5/22/2009	Marcus Delatte
Biopharm	NA	NA	NA
LNC	Acceptable	3/30/2009	Felicia Duffy
Methods Validation	Validation is not required by FDA Lab	6/30/2009	Xiaobin Shen
OPDRA	NA	NA	NA
EA	Acceptable	3/30/2009	Xiaobin Shen
Microbiology	Acceptable	3/30/2009	James McVey

# The Chemistry Review for NDA 22-439

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls standpoint, the NDA is approvable pending adequate responses to support the outstanding issues summarized at end of this review.

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

### II. Summary of Chemistry Assessments

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

The drug product (b) (4) is a clear, colorless to light-yellow oral solution with a grape odor. It is indicated for (b) (4)

Each 5 mL of the solution contains 5.0 mg of hydrocodone bitartrate, 4 mg of chlorpheniramine maleate, and 60 mg of pseudoephedrine hydrochloride. In addition to the three active pharmaceutical ingredients, (b) (4) contains excipients commonly used in oral solution products (e.g. water, citric acid, sodium citrate, sodium saccharine, sucrose, glycerin, propylene glycol, methylparaben, propylparaben and grape flavor). The commercial (b) (4) is packaged in a 16 fl. oz. white HDPE bottle, its professional sample is packaged in (b) (4) bottle.

The process used to manufacture the commercial product (b) (4) is equivalent to that used for the product used in the clinical studies (b) (4).

There are three drug substances for this NDA: hydrocodone bitartrate, chlorpheniramine maleate and pseudoephedrine hydrochloride.

1- Hydrocodone bitartrate (INN & USAN) was approved by FDA and marketed as Hycodan<sup>®</sup> Syrup since 1988. Hydrocodone is a semi synthetic narcotic antitussive and analgesic. Hydrocodone is a white or slightly yellow-white powder that is soluble in water and slightly soluble in alcohol. It is manufactured by (b) (4) and referenced to DMF (b) (4), which was last reviewed in April, 2009 by Dr. Maria Manzoni and found adequate. The DMF's EES status is acceptable. The drug

## Chemistry Assessment Section

product manufacturer release specifications for hydrocodone bitartrate comply with the USP monograph and include appearance, identification, specific rotation, pH, loss on drying, residue on ignition, chloride, ordinary impurities, organic volatile impurities, assay, related substances (specified and unspecified), residual solvents, and microbial limits.

2- Chlorpheniramine maleate is an OTC monograph item. Chlorpheniramine is an antihistamine drug that prevents released histamine from dilating capillaries and causing edema of the respiratory mucosa. Chlorpheniramine maleate is a white crystalline powder that is freely soluble in water and alcohol. It is manufactured by (b) (4) and referenced to DMF (b) (4). This DMF was reviewed on May 27, 2009 and found inadequate. The (b) (4) in DMF (b) (4) is a potential structural alert for geotoxicity, the DMF holder was notified on June 3, 2009 to reduce the level of (b) (4) to no more than (b) (4) day or conduct a bacterial reverse assay to qualify the proposed specification. The DMF's EES status is pending. The drug product manufacturer release specifications for chlorpheniramine maleate comply with the USP monograph and include appearance, identification, melting range, loss on drying, residue on ignition, assay, related substances (specified and unspecified), residual solvents, and microbial limits.

3- Pseudoephedrine hydrochloride is also OTC monograph item. Pseudoephedrine hydrochloride is an orally active sympathomimetic amine and exerts a decongestant action on the nasal mucosa. Pseudoephedrine hydrochloride is a white to almost white crystalline powder that is freely soluble in water. It is manufactured by (b) (4) and referenced to DMF (b) (4). This DMF was reviewed by Guoping Sun, Ph.D. in Feb. 2008 and deemed adequate. Arthur Shaw, Ph.D. reviewed it last in Aug. 2008 after the DMF was resubmitted in CTD-Q format and also deemed it adequate. The holder's EES status is acceptable. The drug product manufacturer release specifications for pseudoephedrine hydrochloride comply with the USP monograph and include appearance, identification, melting range, pH, specific rotation, loss on drying, residue on ignition, ordinary impurities, assay, related substances (specified and unspecified), organic volatile impurities, residual solvents, heavy metals and microbial limits.

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

The drug product (b) (4) is an oral solution, each commercial package contains 16 fl. oz. and each professional sample contains (b) (4). Each 5 mL of the oral solution contains 5 mg of hydrocodone bitartrate, 4 mg of chlorpheniramine maleate, and 60 mg of pseudoephedrine hydrochloride.

Dosing for adults (b) (4) is 5 mL every 4 to 6 hours as needed but not to exceed 4 doses (20 mL) in 24 hours. (b) (4)

(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 found acceptable.

## Chemistry Assessment Section

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

From the perspective of chemistry, manufacturing and control, this drug product is approvable pending satisfactory responses to the CMC deficiencies listed in Section III of the review summary.

(b) (4) oral solution consists of three active moieties. The first active hydrocodone bitartrate was approved by FDA and marketed as Hycodan<sup>®</sup> Syrup since 1988. The other two actives chlorpheniramine maleate and pseudoephedrine hydrochloride are both OTC monograph articles.

There are CMC requests related to the all three drug substances and the drug product which need to be addressed by the DMF holders or the sponsors (see section III of the review summary). EES status are acceptable for all facilities except that for (b) (4) is pending.

The product's trade name has been changed to (b) (4) and deemed acceptable.

The labeling and package insert are acceptable from CMC perspective with minor comments.

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

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

**B. Endorsement Block**

ChemistName/Date: Xiaobin Shen/07-08-2009

ChemistryTeamLeaderName/Date:

ProjectManagerName/Date:

**C. CC Block****Chemistry Assessment**

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/s/

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Xiaobin Shen  
7/8/2009 04:31:29 PM  
PHARMACIST  
Chemistry review 1

Ali Al-Hakim  
7/8/2009 04:45:31 PM  
CHEMIST

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(b) (4) EVALUATION MEMORANDUM

---

**TO:** NDA 22439 (b) (4) AND 22442  
**FROM:** Xiaobin Shen, Ph.D., Reviewer, Branch II, Division I, ONDQA  
**SUBJECT:** Evaluation of (b) (4) in DMF (b) (4)  
**DATE:** 5/27/2009  
**CC:** Prasad Peri, Ph.D., Pharmaceutical Assessment Lead, Branch II, Division I, ONDQA  
Ali, Al Hakim, Ph.D., Branch Chief, Branch II, Division I, ONDQA

---

Impurity (b) (4) present in hydrocodone bitartrate manufactured in DMF (b) (4) was identified as a potential structural alert in the review of the NDAs referenced above. A pharmtox consult request was made via email routing for the evaluation of (b) (4) as potential structural alert.

At the same time, the evaluation of (b) (4) originated from DMF (b) (4) took place in the DAARP division. The evaluation results deemed (b) (4) as not genotoxic, hence there is no need for Pharmtox in the DPAP division to complete the consult request.

The original consult request and the DAARP evaluation report for (b) (4) is attached to this memo to capture the decision making process.

Xiaobin Shen, Ph.D.  
Reviewer, Branch II, Division I, ONDQA

**OND Division of Pulmonary and Allergy Products**

**NDA: 22-439**

**Applicant: Cypress Pharmaceuticals, Inc.**

**Letter Date: Nov 6, 2008**

**Stamp Date: Nov 7, 2008**

**PDUFA Date: 7-Sep-2009**

**Proposed Proprietary Name:** (b) (4) **Oral Solution**

**Established Name:** Hydrocodone bitartrate, Pseudoephedrine Hydrochloride, and Chlorpheniramine Maleate

**Dosage form and strength:** Oral Solution, 5 mg hydrocodone bitartrate, 60 mg pseudoephedrine hydrochloride, and 4 mg Chlorpheniramine maleate each, in 5 mL.

**Route of Administration:** Oral

**Indications:** Indicated for (b) (4)

**Dose:** Adults (b) (4) : (b) (4) (5 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: Xiaobin Shen, Ph.D.

**Time goals:**

**Initial Quality Assessment in DFS: by 15-Dec-2008**

**Chemistry filing memo in DFS: by 6-Jan-2009 (after filing meeting)**

Filing decision "Day 60": **6-Jan-2009**

Filing Date "Day 74": 20-Jan-2009

**Chemistry Review (DR/IR) letter: by 8-Apr-2009**

Mid-cycle meeting "Month 5": 31-Mar-2009

**Final Chemistry Review "Month 8" in DFS: by 31-Jul-2009**

Wrap-Up Meeting (end of mo 8): **June 29, 2009**

Primary Review (1 wk after WU): **July 31, 2009**

Secondary Review (6 wks before Action): ~ **Jul 25th, 2009**

Labeling Tcon (5 wks before Action): **Jul 30, 2009**

CDTL Memo (4 wks before Action): **Aug 7, 2009**

**PDUFA: 7-Sept-2009**

**Related Documents**

**INDs pertaining to this are:** (b) (4)

**NDA's pertaining to this are:** None

USAN/INN/JAN	<b>Chlorpheniramine Maleate</b>
Chemical Name	2-Pyridinepropanamine, $\gamma$ -(4-chlorophenyl)- <i>N,N</i> -dimethyl-, ( <i>Z</i> )-2-butenedioate (1:1) 2-[ <i>p</i> -Chloro- $\alpha$ -[2-(dimethylamino)ethyl]benzyl]pyridine maleate (1.1)
CAS #	113-92-8
Molecular Formula	C <sub>16</sub> H <sub>19</sub> ClN <sub>2</sub> ·C <sub>4</sub> H <sub>4</sub> O <sub>4</sub>
Molecular weight	390.86

Melting Range	130-135°C
Structure	

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 <sub>10</sub> H <sub>14</sub> NO <sub>4</sub> HCl
Molecular weight	201.69
Structure	

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 (1 : 1) hydrate (2:5)
CAS #	143-71-5 (anhydrous) 34195-34-1 (Hydrocodone Bitartrate)
Molecular formula	C <sub>18</sub> H <sub>21</sub> N <sub>03</sub> . C <sub>4</sub> H <sub>6</sub> O <sub>6</sub> . 2 1/2 H <sub>2</sub> O
Molecular weight	494.490
Structure	

CONSULTS/ CMC RELATED REVIEWS	COMMENT
Clinical Pharm (BA/BE) - Dissolution	No Applicable
CDRH	Not Applicable
EA	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 electronic 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 (Chlorpheniramine maleate and pseudoephedrine hydrochloride) 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 and Hycomine. The NDA is based on a PK bioavailability and food effect 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 dihydrate is a white or slightly yellow-white color powder. It is fairly soluble in water and but not soluble in ether and chloroform and pH of a 2% Aqueous solution is about 3.6. 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 sponsor states that they have not yet identified (b)(4) in their drug product. 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)/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 reviewed for safety during the IND review by Dr. Art Shaw (date 8/14/2008) and previously for an NDA by Dr. Guoping Sun (date 2/26/2008). The GSL drug substance specification complies with the USP monograph for pseudoephedrine hydrochloride, ICH Q3C(R3) for residual solvents, and with the ICH Q3A(R2) qualification limit for

related substances. The limits for total aerobic counts and total combined yeast and molds counts are those required by USP <1111>.

- Chlorpheniramine maleate USP, 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 Dr. Guoping Sun (date 6/25/2008). and found adequate for a solid, oral dosage form. Since that review, and Deficiency letter was sent to the DMF holder and an amendment was received on 7/9/2008. This amendment will need to be reviewed.
- The lots of drug product used for clinical trial and registration 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.

### Drug Product

- Drug Product is an aqueous solution containing (b)(4) sucrose and (b)(4) sodium saccharine with a grape flavoring agent. It is a clear, colorless to light yellow liquid with a grape odor and free of any precipitates.
- The registration batches are (b)(4) size while the proposed commercial scale is stated to be (b)(4). All excipients are USP or NF grade with the exception of the grape flavor. 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.

Table 3.2.P.1-1. Unit Composition of (b)(4) Oral Solution					
Component	Reference to Quality Standards	Function	Unit Composition		
			% w/v	mg/mL	mg/480 mL
Hydrocodone Bitartrate	USP	Active ingredient	(b)(4)	1.0	480
Chlorpheniramine Maleate	USP	Active ingredient	(b)(4)	0.8	384
Pseudoephedrine Hydrochloride	USP	Active ingredient	(b)(4)	12.0	5760
Citric Acid, Anhydrous	USP	(b)(4)	(b)(4)	(b)(4)	(b)(4)
Sodium Citrate	USP				
Sodium Saccharin	USP				
Methylparaben	NF				
Propylparaben	NF				
Sucrose	NF				
Glycerin (b)(4)	USP				
Propylene Glycol	USP				
Grape Flavor (b)(4)	In-house				
Water, Purified	USP				

NF = National Formulary.

Table 3.2.P.1-2. Container Closure for (b) (4) Oral Solution	
Component	Professional Sample (b) (4) Commercial Product (480 mL)
Container	(b) (4) bottle with a (b) (4) neck finish
Closure	(b) (4)
(b) (4)	

- Drug product is manufactured at by (b) (4). The methods of manufacturing are relatively straight forward. (b) (4)
- The in process tests used are pH, appearance, density, and viscosity. (b) (4)
- The product is filled into (b) (4) Bottle with (b) (4) Neck finish (b) (4) and 16 ounce, white HDPE bottles (b) (4).
- Drug product specifications are listed on the following page along with the results for three batches.
- Stability data for three batches at accelerated and long term storage conditions are provided. For both the conditions, **only 3 months of data** are provided and the sponsor has not proposed any shelf life in the application.
- The reviewer needs to evaluate the provided data and may propose a (b) (4) shelf life for the drug product based on the available data. Note that ICH Q1A only allows a 12 months extrapolation of stability data, if the data are robust.
- The sponsor mentions that no leachables are observed in the drug product.

### 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.
- **Dose Dumping.** Not applicable.
- **Microbial Testing:**  
It is not clear if the sponsor has done a (b) (4). The reviewer should evaluate the possibility of consulting microbiology staff if this is an issue.

#### **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. The registration stability batches are (b) (4) and the proposed commercial batches are (b) (4).
- **GMP status of the drug substance/drug product manufacturing sites.**

Note that the (b) (4) was found acceptable based on profile. (b) (4) sites are sent to the DO for evaluation. (b) (4) (Drug product manufacturing site) was assigned for inspection.

- **Safety of imprinting inks**  
Although the sponsor claims no leachables, there are several extractables that will need to be evaluated in this NDA. The sponsor has not proposed acceptance criteria for leachables.
- **Dissolution of the drug product**  
Not applicable
- **Degradation products in the drug product:** The sponsor claims no degradation products in the stability data provided.
- **Sensitivity of product to moisture and light.** This is an aq. solution packaged in (b) (4) and HDPE bottles. There is a possibility of degradants. The sponsor claims the color of the product to be slightly yellow however, no explanation on why the color is provided.
- **Weight Loss:** None proposed.
- **Shelf life:** None proposed. Will need to be evaluated by reviewer.
- **Bulk Drug Product Stability Packaging Data and Protocol**  
(b) (4)
- **Comparability Protocol:** None proposed.
- **Stability: The stability data provided are on 3 months of accelerated and long term.**
- The first three consecutive commercial batches will be placed on stability.

Test	Acceptance Criterion	Stability Result (Range of Values)			
		Long-Term (Up to 3 Months)	Accelerated (Up to 3 Months)	Photostability	Thermal Cycle (4 Cycles)
Description	Clear, colorless to light yellow liquid with a grape odor and free from precipitation	Conforms	Conforms	Conforms	Conforms
pH (25 °C)		(b) (4)			
Color					
Viscosity (25 °C)					
Hydrocodone Bitartrate Assay					
Chlorpheniramine Maleate Assay					
Pseudoephedrine Hydrochloride Assay					
Methylparaben Assay					
Propylparaben Assay					
Impurities/Degradants: Specified Known Impurities:	(b) (4)				
Individual Unspecified Impurities					
Total Impurities					

**Table 2.3.P-16. Summary of Stability Results for Registration Batch 00658/P08001 (16 oz/480 mL)**

Test	Acceptance Criterion	Stability Result (Range of Values)			
		Long-Term (Up to 3 Months)	Accelerated (Up to 3 Months)	Photostability	Thermal Cycle (4 Cycles)
Microbial Limit: Total Aerobic Count					
Total Yeasts and Molds					
<i>E. coli</i>					
<i>P. aeruginosa</i>					
<i>Staph. aureus</i>					
<i>Salmonella</i> spp.					
Weight loss					
Packaging	Closure and seal intact, no leak	Conforms	Conforms	Conforms	Conforms
ND = Not detected. NT = Not tested.					

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

**Table 3.2.P.7-1. Container Closure and Material of Construction**

Component	Commercial Product (480 mL)	Professional Sample
Container:		
Material of Construction		
Closure:		
Material of Construction: Outer cap		
Inner cap		
Liner		

ONDQA PAL's Initial Quality Assessment  
Prasad Peri, Ph.D., Division of Pre-Marketing Assessment 1, Branch 2

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DMF	TYPE	HOLDER	ITEM REFERENCED	COMMENTS
(b) (4)	II			(b) (4) 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			Review Needed. Direct food contact regulations needed for components.
	III			Review Needed. Direct food contact regulations needed for components.
	III			Adequate for Oral Solution in review dated 9/1/1999. Direct food contact regulations needed for components.
	III			Adequate for solid oral dosage forms. Complies with food contact regulations as listed in 21 CFR 177.1520 178.3297 and 181.5

<b>Table 2.3.P-4. Specifications for REZIRA-CC Oral Solution</b>					
Test	Acceptance Criterion		Analytical Procedure		
	Release	Stability			
Appearance/Description	Clear, colorless to light yellow liquid with a grape odor and free from precipitation	Clear, colorless to light yellow liquid with a grape odor and free from precipitation	Visual		
Color	(b) (4)		SOP-QC-300		
Density <sup>a,b</sup>			USP <841>		
Viscosity <sup>a</sup>			USP <911>		
pH <sup>a</sup>			USP <791>		
Deliverable Volume <sup>b,c</sup>			USP <698>		
Identification A: <sup>b</sup> Hydrocodone Bitartrate, Chlorpheniramine Maleate, and Pseudoephedrine Hydrochloride					SOP-QC-287
Identification B: <sup>b</sup> Hydrocodone Bitartrate, Chlorpheniramine Maleate, and Pseudoephedrine Hydrochloride					
Assay: Hydrocodone Bitartrate (5 mg/5 mL)					SOP-QC-287
Chlorpheniramine Maleate (4 mg/5 mL)					
Pseudoephedrine Hydrochloride (60 mg/5 mL)					

Table 2.3.P-4. Specifications for (b) (4) Oral Solution				
Test	Acceptance Criterion		Analytical Procedure	
	Release	Stability		
Methylparaben (b) (4)	(b) (4)		(b) (4)	
Propylparaben (b) (4)				
Specified Impurity: (b) (4)				
Individual Unspecified Impurities				
Total Impurities				
Antimicrobial Effectiveness Test <sup>d</sup>				USP <51>
Total Combined Molds and Yeast Count				USP <61>
Total Aerobic Microbial Count				USP <61>
<i>Salmonella</i> species				
<i>Escherichia coli</i>				
<i>Pseudomonas aeruginosa</i>				
<i>Staphylococcus aureus</i>				
Packaging				Visual
(b) (4)				NA
<sup>a</sup> = Performed on bulk solution (for release). <sup>b</sup> = Performed at release only. <sup>c</sup> = Performed on professional samples ((b) (4) bottles) for release testing only. <sup>d</sup> = This test will be performed on the stability samples of the commercial batch (b) (4) (b) (4)				
LC = Label claim. NA = Not applicable.				

• **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		
6	Has an environmental assessment report or categorical exclusion been provided?	X		Applicant shows calculations of less than the specified amount listed in the regulations. Consult to be sent
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	3 months stability data provided. No shelf life proposed
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 to be provided and evaluated
16	Is a production batch record provided	X		

**Draft CMC Comments for 74 day Letter**

- 1. Provide references to direct food additive regulations for all the packaging materials (bottles, (b) (4) closures, etc.) that are in contact with the formulation.**
- 2. 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. We strongly encourage you to use appropriate analytical methods that are capable of monitoring and separate these compounds from other degradants and impurities in the drug product. Leachables specifications will be applied when the data in your drug product have reached an asymptote.**
- 3. We note that you have provided only 3 months long term and accelerated stability data for your drug product. We also note that you have not proposed a shelf life for your drug product. Based on the stability data in your NDA, you could potentially get a shelf life equal to the available real time data. It is inappropriate to set final specification based on the available stability data. This is a potential review issue as you will need to generate stability data to be able to assess trends in attributes listed in your drug product specifications.**
- 4. Provide the CMC information (qualitative and quantitative composition, stability data etc.) of the comparison drug products: pseudoephedrine hydrochloride oral solution and chlorpheniramine maleate oral solution. If this information has already been provided, provide a reference to the section and page number in your NDA.**
- 5. Provide a quantitative and qualitative chemical composition of the grape flavor (b) (4). Alternately this information may be provided in an authorized Drug Master File (DMF).**
- 6. Provide results of your Antimicrobial Effectiveness testing for your drug product.**
- 7. 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  
12/11/2008 12:24:18 PM  
CHEMIST

Ali Al-Hakim  
12/11/2008 12:40:49 PM  
CHEMIST

**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT**

<b>Application:</b>	NDA 22439/000	<b>Sponsor:</b>	CYPRESS PHARM
<b>Office:</b>	570		135 INDUSTRIAL BLVD
<b>Priority:</b>	4S		MADISON, MS 39110
<b>Stamp Date:</b>	07-NOV-2008	<b>Brand Name:</b>	(b) (4) (HYDROCODONE BITARTRATE/CHLORPH
<b>PDUFA Date:</b>	07-SEP-2009	<b>Estab. Name:</b>	
<b>Action Goal:</b>		<b>Generic Name:</b>	HYDROCODONE, CHLORPHENIRAMINE, PSE
<b>District Goal:</b>	09-JUL-2009	<b>Product Number; Dosage Form; Ingredient; Potency</b>	

<b>FDA Contacts:</b>	P. BOWEN	Project Manager	(HFD-570)	301-796-2466
	P. PERI	Review Chemist	(HFD-820)	301-796-1730
	A. AL HAKIM	Team Leader		301-796-1323

**Overall Recommendation:** ACCEPTABLE on 31-AUG-2009 by E. JOHNSON (HFD-320) 301-796-3334

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

**DMF No:** [REDACTED] **AADA:**

**Responsibilities:** DRUG SUBSTANCE MANUFACTURER  
DRUG SUBSTANCE PACKAGER  
DRUG SUBSTANCE RELEASE TESTER  
DRUG SUBSTANCE STABILITY TESTER

**Profile:** [REDACTED] (b) (4) **OAI Status:** NONE

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 23-DEC-2008

**Decision:** ACCEPTABLE

**Reason:** BASED ON PROFILE

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

**DMF No:** [REDACTED] **AADA:**

**Responsibilities:** DRUG SUBSTANCE OTHER TESTER  
FINISHED DOSAGE OTHER TESTER

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

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 05-DEC-2008

**Decision:** ACCEPTABLE

**Reason:** BASED ON PROFILE

**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT**

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

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER  
DRUG SUBSTANCE PACKAGER  
DRUG SUBSTANCE RELEASE TESTER  
DRUG SUBSTANCE STABILITY TESTER

Profile: (b) (4) OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 05-DEC-2008

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

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

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE OTHER TESTER  
FINISHED DOSAGE MANUFACTURER  
FINISHED DOSAGE PACKAGER  
FINISHED DOSAGE RELEASE TESTER  
FINISHED DOSAGE STABILITY TESTER

Profile: (b) (4) OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 29-JUN-2009

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

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FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT

Establishment: CFN: (b) (4) FEI: (b) (4)  
(b) (4)  
DMF No: AADA:  
Responsibilities: DRUG SUBSTANCE MANUFACTURER  
DRUG SUBSTANCE PACKAGER  
DRUG SUBSTANCE RELEASE TESTER  
DRUG SUBSTANCE STABILITY TESTER  
Profile: (b) (4) OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 31-AUG-2009  
Decision: ACCEPTABLE  
Reason: DISTRICT RECOMMENDATION

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Establishment: CFN: (b) (4) FEI: (b) (4)  
(b) (4)  
DMF No: AADA:  
Responsibilities: FINISHED DOSAGE OTHER TESTER  
CONTROL TESTING LABORATORY OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 05-DEC-2008  
Decision: ACCEPTABLE  
Reason: BASED ON PROFILE

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