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: (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 Zutripro 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.

EES Status:
Recommendations: Acceptable

Consults:
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 and referenced to DMF. The DMF was reviewed and found acceptable (dated 12/14/2010).
- **Pseudoephedrine hydrochloride** USP is made by Information is presented in DMF. This DMF was reviewed and found acceptable (review dated 8/3/2010)
- **Chlorpheniramine maleate** USP is obtained from. The drug substance is referenced to DMF. 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-, (5α)-, [R-(R*,R*)]-2,3-dihydroxybutanedioate (1:1), hydrate (2:5)

![Hydrocodone bitartrate Structure](image)

**Molecular Formula:** C_{18}H_{21}NO_3·C_{4}H_{6}O_6·2\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)

![Chemical Structure of Chlorpheniramine Maleate]

Molecular Formula: \(\text{C}_{16}\text{H}_{15}\text{ClN}_2\cdot\text{C}_4\text{H}_4\text{O}_4\)
Molecular Weight: 390.86

Pseudoephedrine hydrochloride
Chemical Name: a-[1-(methylamino)ethyl]-[S-(R*,R*)] hydrochloride; (+)-Pseudoephedrine hydrochloride; Benzenemethanol and Dpseseudoephedrine hydrochloride

![Chemical Structure of Pseudoephedrine Hydrochloride]

Molecular Formula: \(\text{C}_{10}\text{H}_{15}\text{NO} \cdot \text{HCl}\)
Molecular Weight: 201.69

Conclusion: The drug substances are satisfactory.

Drug Product:
The drug product is manufactured by [manufacturer]. The methods of manufacturing are relatively straightforward. Inactive excipients include water, citric acid, sodium citrate, sodium saccharine, sucrose, glycerin, propylene glycol, methylparaben, propylparaben and grape flavor. The in-process tests used are pH, appearance, density, and viscosity. The commercial
Zutriprois 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, antimicrobial effectiveness test, microbial limit tests, total yeast and mold, 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
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

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
# Table of Contents

Table of Contents ................................................................................................................................................. 2

Chemistry Review Data Sheet ................................................................................................................................. 3

The Executive Summary ........................................................................................................................................... 9

I. Recommendations .................................................................................................................................................. 9
   A. Recommendation and Conclusion on Approvability ....................................................................................... 9
   B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable .......................................................................................................................... 9

II. Summary of Chemistry Assessments .................................................................................................................... 9
   A. Description of the Drug Product(s) and Drug Substance(s) ........................................................................ 9
   B. Description of How the Drug Product is Intended to be Used ...................................................................... 11
   C. Basis for Approvability or Not-Approval Recommendation ......................................................................... 11

III. Administrative ...................................................................................................................................................... 11
   A. Reviewer’s Signature ....................................................................................................................................... 12
   B. Endorsement Block ........................................................................................................................................... 12
   C. CC Block ............................................................................................................................................................ 12

Chemistry Assessment .............................................................................................................................................. 13

I. Review Of Quality Information Amendment SN 0020 ......................................................................................... 13

II. Final Drug Substance Release Specifications ...................................................................................................... 19
   A. Hydrocodone Bitartrate .................................................................................................................................. 19
   B. Chlorpheniramine Maleate .............................................................................................................................. 20
   C. Pseudoephedrine Hydrochloride ....................................................................................................................... 21

III. Drug Product Release and Stability Specifications for Commercial Batches .................................................... 22

IV. Nanomaterial Information Table ........................................................................................................................ 23
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:

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1. Contains no CMC information.

6. SUBMISSION(S) BEING REVIEWED:
CHEMISTRY REVIEW

Chemistry Review Data Sheet

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7. NAME & 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 110th 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

Chemistry Review Data Sheet

a) Proprietary Name: Zutrip®
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® 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:  _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:**
4,5α-Epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5)

![Hydrocodone Bitartrate structure]

Molecular Formula: C_{18}H_{21}NO_{3}·C_{4}H_{6}O_{6}·2\frac{1}{2}H_{2}O
Molecular Weight: 494.490

**Chlorpheniramine Maleate:**
2-Pyridinepropanamine, γ-(4-chlorophenyl)-N,N-dimethyl-, (Z)-2-butenedioate (1:1)

![Chlorpheniramine Maleate structure]

Molecular Formula: C_{16}H_{19}ClN_{2}·C_{4}H_{4}O_{4}
Molecular Weight: 390.86

**Pseudoephedrine Hydrochloride:**
[S-(R*,R*)]-α-[1-(methylamino)ethyl]-benzenemethanol hydrochloride
Molecular Formula: C_{10}H_{15}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:

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1. 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”)

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

B. Other Documents:

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18. STATUS:

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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

   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 saccharin, 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 bottle.

   The process used to manufacture the commercial product is equivalent to that used for the product used in the clinical studies. The product is manufactured by . Microbial limit testing is performed by . Testing of raw materials is performed by . 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. Specified impurities 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
impurity at \( \leq \) still within the 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® 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 \( \text{[Redacted]} \) and referenced to DMF \( \text{(b)(4)} \), 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 \( \text{[Redacted]} \). The retest date is \( \text{[Redacted]} \) 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 \( \text{[Redacted]} \) and referenced to DMF \( \text{(b)(4)} \). This DMF was reviewed on May 27, 2009 and found inadequate. The \( \text{[Redacted]} \) in DMF \( \text{(b)(4)} \) was identified as a potential structural alert for genotoxicity, the DMF holder was notified on June 3, 2009 to reduce the level of \( \text{[Redacted]} \) to no more than \( \text{[Redacted]} \) /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), \( \text{[Redacted]} \). Chlorpheniramine maleate drug substance is packaged in \( \text{[Redacted]} \). The retest date is \( \text{[Redacted]} \) 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 \( \text{[Redacted]} \) and referenced to DMF \( \text{(b)(4)} \). 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.
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), and unspecified. Pseudoephedrine hydrochloride drug substance is packaged in [ ](O). The retest date is [ ](O) 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 [ ](O). 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 [ ](O) is 5 mL every 4 to 6 hours as needed but not to exceed 4 doses (20 mL) in 24 hours. [ ](O) 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® 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

12 Page(s) has been Withheld in Full as B4 (CCL/TS) immediately following this page
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

XIAOBIN SHEN
04/12/2011
The NDA is recommended for approval from CMC perspective.

PRASAD PERI
04/12/2011
I concur
NDA 22-439

(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
# Table of Contents

Table of Contents ........................................................................................................... 2

Chemistry Review Data Sheet ......................................................................................... 3

The Executive Summary .................................................................................................. 9

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   A. Recommendation and Conclusion on Approvability ............................................. 9
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   B. Endorsement Block ........................................................................................... 12
   C. CC Block .......................................................................................................... 12

Chemistry Assessment .................................................................................................... 13

I. Review Of Quality Information Amendment SN 0009 .............................................. 13
   I.1 Responses to the Complete Response Letter, September 18, 2009 .................... 13
   I.2 Additional Responses to the Information Request Letter, April 30, 2009 .......... 15
   I.3 Responses to Facsimile Letter, June 3, 2009 ....................................................... 16
   I.4 Additional (Minor) Revisions ............................................................................. 18

II. Review Of Quality Information Amendment SN 0010, 0011, and 0012 ......... 18
   II.1 Responses to Information Request on 26-Mar-2010 .......................................... 18

III. Revised Chlorpheniramine Maleate and Drug Product Specifications ................ 18

IV. List Of Comments .................................................................................................... 21
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:

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¹. Contains no CMC information.

7. NAME & ADDRESS OF APPLICANT:
8. **DRUG PRODUCT NAME/CODE/TYPE:**

   a) Proprietary Name: [Redacted] 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® 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 ___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:  
   4,5α-Epoxo-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5)
Molecular Formula: C_{18}H_{21}NO_{5} \cdot C_{4}H_{6}O_{6} \cdot 2\frac{1}{2}H_{2}O  
Molecular Weight: 494.490

**Chlorpheniramine Maleate:**
2-Pyridinepropanamine, γ-(4-chlorophenyl)-N,N-dimethyl-, (Z)-2-butenedioate (1:1)

![Molecular Structure of Chlorpheniramine Maleate](image)

Molecular Formula: C_{18}H_{19}ClN_{2} \cdot C_{4}H_{4}O_{4}  
Molecular Weight: 390.86

**Pseudoephedrine Hydrochloride:**
[S-(R*,R*)]-α-[1-(methylamino)ethyl]-benzenemethanol hydrochloride

![Molecular Structure of Pseudoephedrine Hydrochloride](image)

Molecular Formula: C_{10}H_{15}NO \cdot HCl  
Molecular Weight: 201.69  
*Comment:* The applicant provided chemical name is incorrect: α-[1-(methylamino)ethyl]-[S-(R*,R*)] hydrochloride.

### 17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

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### Chemistry Review Data Sheet

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| II | 3 | Adequate | 15-Oct-2009 | The DMF is deemed adequate in support of an oral solution |
| III | 4 | Adequate | 26-Mar-2010 | The review deemed it adequate in support of an oral solution |
| III | 4 | Adequate | 26-Mar-2010 | The review deemed it adequate in support of an oral solution |

### Action codes for DMF Table:
1. DMF Reviewed.
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")

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

   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, 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 is packaged in a 16 fl. oz. white HDPE bottle, its professional sample is packaged in bottle.

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

   Specified impurities 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
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) (c) 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) (c) 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® 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) (c) and referenced to DMF (b) (c), 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) (c). The retest date is (b) (c) 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) (c) and referenced to DMF (b) (c). This DMF was reviewed on May 27, 2009 and found inadequate. The (b) (c) in DMF (b) (c) was identified as a potential structural alert for genotoxicity, the DMF holder was notified on June 3, 2009 to reduce the level of (b) (c) to no more than (b) (c)/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) (c). The retest date is (b) (c) 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 [3] and referenced to DMF [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 [5]. The retest date is [6] from the manufacturing date.

B. Description of How the Drug Product is Intended to be Used
The drug product [7] is an oral solution, each commercial package contains 16 fl. oz. and each professional sample contains [8]. 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 [9] is 5 mL every 4 to 6 hours as needed but not to exceed 4 doses (20 mL) in 24 hours. [10] 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.

[11] oral solution consists of three active moieties. The first active hydrocodone bitartrate was approved by FDA and marketed as Hycodan® 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 [REDACTED]. 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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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

XIAOBIN SHEN
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

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

Cypress Pharmaceuticals, Inc.

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

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6. SUBMISSION(S) BEING REVIEWED:

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7. NAME & ADDRESS OF APPLICANT:

Name: Cypress Pharmaceuticals, Inc.
CHEMISTRY REVIEW

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 110th 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: [Redacted]
      Oral Solution (proposed); It is later changed to [Redacted]
   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® 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

   ___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:
   4,5α-Epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5)

   ![Chemical Structure](image-url)
Molecular Formula: C₁₈H₂₁NO₃·C₄H₆O₆·2½H₂O  
Molecular Weight: 494.490

**Chlorpheniramine Maleate:**
2-Pyridinepropanamine, \( \gamma \)-\((4\text{-chlorophenyl})-N,N\text{-dimethyl-}, \ (Z)-2\text{-butenedioate} \) (1:1)

Molecular Formula: C₁₆H₁₉ClN₂·C₄H₄O₄  
Molecular Weight: 390.86

**Pseudoephedrine Hydrochloride:**
\([S-(R^*,R^*)]-\alpha-[1\text{-}(methylamino)ethyl]-\text{benzenemethanol hydrochloride}\)

Molecular Formula: C₁₀H₁₅NO·HCl  
Molecular Weight: 201.69

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

17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

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1 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")

2 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

Chemistry Review Data Sheet

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Page 8 of 24
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 [REDACTED] is a clear, colorless to light-yellow oral solution with a grape odor. It is indicated for

   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, [REDACTED] contains excipients commonly used in oral solution products (e.g. water, citric acid, sodium citrate, sodium saccharin, sucrose, glycerin, propylene glycol, methylparaben, propylparaben and grape flavor). The commercial [REDACTED] is packaged in a 16 fl. oz. white HDPE bottle, its professional sample is packaged in [REDACTED] bottle.

   The process used to manufacture the commercial product [REDACTED] is equivalent to that used for the product used in the clinical studies [REDACTED].

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® 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 [REDACTED] and referenced to DMP [REDACTED], which was last reviewed in April, 2009 by Dr. Maria Manzoni and found adequate. The DMF's EES status is acceptable. The drug
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).

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 [name redacted] and referenced to DMF [redacted]. This DMF was reviewed on May 27, 2009 and found inadequate. The [name redacted] in DMF [redacted] is a potential structural alert for genotoxicity, the DMF holder was notified on June 3, 2009 to reduce the level of [redacted] to no more than [redacted]/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 [name redacted] and referenced to DMF [redacted]. 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 [name redacted] is an oral solution, each commercial package contains 16 fl. oz. and each professional sample contains [redacted]. 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 [redacted] is 5 mL every 4 to 6 hours as needed but not to exceed 4 doses (20 mL) in 24 hours. 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.

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.

[redacted]
oral solution consists of three active moieties. The first active hydrocodone bitartrate was approved by FDA and marketed as Hycodan® 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 [redacted]. This site was inspected and currently pending on inspection recommendation.

The product’s trade name has been changed to [redacted] 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

13 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page
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<th>Submission Type/Number</th>
<th>Sponsor Name</th>
<th>Drug Name / Subject</th>
</tr>
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</table>
| NDA 22439           | ORIG 1                 | CYPRESS PHARMACEUTICAL INC | (HYDROCODONE BITARTRATE/CHLORPH |}

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

/s/

XIAOBIN SHEN
08/31/2009

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

(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.

EES Status: Recommendations: Acceptable
Consults: 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 . The DMF was reviewed and found acceptable (review dated 04/07/2009).
- **Pseudoephedrine hydrochloride** USP is made by . Information is presented in DMF . This DMF was reviewed and found acceptable (review dated 8/13/2008)
- **Chlorpheniramine maleate** USP is obtained from . The drug substance is referenced to DMF . This DMF was reviewed on May 27, 2009 and found inadequate. The in DMF is a potential structural alert for geontoxicity, the DMF holder was notified on June 3, 2009 to reduce the level of to no more than /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-, (5α)-, [R-(R*,R*)]-2,3-dihydroxybutanedioate (1:1), hydrate (2:5)

![Hydrocodone bitartrate structure]

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 Structure](image)

Molecular Formula: \(C_{10}H_{15}ClN_{2}C_{4}H_{4}O_{4}\)
Molecular Weight: 390.86

**Pseudoephedrine hydrochloride**

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

![Molecular Structure](image)

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

The methods of manufacturing are relatively straight forward.

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

The in process tests used are pH, appearance, density, and viscosity. The commercial
is packaged in a 16 fl. oz. white HDPE bottle, its professional sample is packaged in _______ bottle.

Drug product specifications include Appearance, color, density, viscosity, deliverable volume, weight loss, identification, impurities, _______ 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
- Deficiencies for hydrocodone bitartrate drug substance (impurities and related specifications)
- Test data for stability and microbial testing
- 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

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/
---------------------
Ali Al-Hakim
7/14/2009 10:42:20 AM
CHEMIST
NDA 22-439

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

Cypress Pharmaceuticals, Inc.

Xiaobin Shen, Ph.D.
Division of Pulmonary and Allergy Drug Products
# Table of Contents

Table of Contents .................................................................................................................. 2

Chemistry Review Data Sheet ............................................................................................. 4

The Executive Summary ....................................................................................................... 10

I. Recommendations .......................................................................................................... 10
   A. Recommendation and Conclusion on Approvability .................................................. 10
   B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk
      Management Steps, if Approvable ................................................................................. 10

II. Summary of Chemistry Assessments ............................................................................. 10
   A. Description of the Drug Product(s) and Drug Substance(s) ..................................... 10
   B. Description of How the Drug Product is Intended to be Used .................................... 11
   C. Basis for Approvability or Not-Approval Recommendation ...................................... 12

III. Administrative ............................................................................................................... 12
   A. Reviewer’s Signature ................................................................................................. 12
   B. Endorsement Block .................................................................................................. 12
   C. CC Block .................................................................................................................. 12

Chemistry Assessment ........................................................................................................ 12

   S DRUG SUBSTANCE – Hydrocodone Bitartrate, .................................................. 13
   S DRUG SUBSTANCE – Chlorpheniramine Maleate, ................................................. 29
   S DRUG SUBSTANCE – Pseudoephedrine Hydrochloride, ...................................... 35
   P DRUG PRODUCT [Oral Solution] ................................................................................ 45
   A APPENDICES ........................................................................................................... 84
   R REGIONAL INFORMATION ..................................................................................... 84

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1 .......................... 85
   A. Labeling & Package Insert ...................................................................................... 85
   B. Environmental Assessment Or Claim Of Categorical Exclusion ............................... 88

III. List Of Deficiencies To Be Communicated .................................................................. 88
IV. Post Mid-Cycle Review ........................................................................................................... 91

S DRUG SUBSTANCE – Hydrocodone Bitartrate ........................................................................... 91

S DRUG SUBSTANCE – Chlorpheniramine Maleate ...................................................................... 91

P8 STABILITY DATA SUBMITTED ON MAY 19, 2009 ................................................................ 91

EVALUATION OF APPLICANT RESPONSES IN MAY 2009 TO THE FILING
COMMUNICATION LETTER DATED JANUARY 16, 2009 ................................................................. 96
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:

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6. SUBMISSION(S) BEING REVIEWED:

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<td>Amendment 0001</td>
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<tr>
<td>Amendment 0007</td>
<td>05/19/2009</td>
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7. NAME & 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 110th 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: [Redacted] Oral Solution (proposed); It is later changed to [Redacted]
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® Syrup, 5 mg/5 mL, NDA 005213, Endo Pharmaceuticals.
Chlorpheniramine Maleate — OTC monograph.
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:**
    4,5α-Epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5)
Chemistry Review Data Sheet

Molecular Formula: C₁₈H₂₁NO₅•C₄H₆O₆•2½H₂O
Molecular Weight: 494.490

Chlorpheniramine Maleate:
2-Pyrindinepropanamine, γ-(4-chlorophenyl)-N,N-dimethyl-, (Z)-2-butenedioate (1:1)

Molecular Formula: C₁₆H₁₅ClN₂•C₄H₄O₄
Molecular Weight: 390.86

Pseudoephedrine Hydrochloride:
[S-(R*,R*)]-α-[1-(methylamino)ethyl]-benzenemethanol hydrochloride

Molecular Formula: C₁₀H₁₃NO•HCl
Molecular Weight: 201.69
Comment: The applicant provided chemical name is incorrect: \( \alpha-[1-\text{methylamino})\text{ethyl}]-[S-(R^*,R^*)] \) hydrochloride.

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

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CHEMISTRY REVIEW

Chemistry Review Data Sheet

1 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")

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

B. Other Documents:

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<td>IND</td>
<td>102177</td>
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18. STATUS:

ONDQA:

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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 is a clear, colorless to light-yellow oral solution with a grape odor. It is indicated for

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, 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 is packaged in a 16 fl. oz. white HDPE bottle, its professional sample is packaged in bottle.

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

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 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 and referenced to DMF, which was last reviewed in April, 2009 by Dr. Maria Manzioni and found adequate. The DMF’s EES status is acceptable. The drug
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 diluting 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 [company name] and referenced to DMF [number]. This DMF was reviewed on May 27, 2009 and found inadequate. The [issue] in DMF [number] is a potential structural alert for genotoxicity, the DMF holder was notified on June 3, 2009 to reduce the level of [issue] to no more than [number] 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 [company name] and referenced to DMF [number]. 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 [description] is an oral solution, each commercial package contains 16 fl. oz. and each professional sample contains [description]. 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 [description] is 5 mL every 4 to 6 hours as needed but not to exceed 4 doses (20 mL) in 24 hours. [description] 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.
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® 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

90 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

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

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

TO: NDA 22439 AND 22442
FROM: Xiaobin Shen, Ph.D., Reviewer, Branch II, Division I, ONDQA
SUBJECT: Evaluation of ___________ in DMF
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 ___________ present in hydrocodone bitartrate manufactured in DMF ___________ was identified as a potential structural alert in the review of the NDAs referenced above. A pharmtex consult request was made via email routing for the evaluation of ___________ as potential structural alert.

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

The original consult request and the DAARP evaluation report for ___________ 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: 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 (5 mL) every 4 hours, not to exceed 4 doses in 24 hours.

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
  - Labeling Tcon (5 wks before Action): Jul 30, 2009
- **PDUFA:** 7-Sept-2009

**Related Documents**

- **INDs pertaining to this are:** None
- **NDAs pertaining to this are:** None

### USAN/INN/JAN | Chlorpheniramine Maleate
<p>| Chemical Name | 2-Pyridinepropanamine, γ-(4-chlorophenyl)-N,N-dimethyl-, (Z)-2-butenedioate (1:1) 2-[p-Chloro-a-[2-(dimethylamino)ethyl]benzyl]pyridine maleate (1:1) |
| CAS #         | 113-92-8 |
| Molecular Formula | C16H19ClN2·C4H4O4 |
| Molecular weight | 390.86 |</p>
<table>
<thead>
<tr>
<th>USAN/INN/JAN</th>
<th>Pseudoephedrine Hydrochloride USP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical Name</td>
<td>Benzenemethanol, a-(1-(methylamino)ethyl)-(S-(R*,R*)J , hydrochloride</td>
</tr>
<tr>
<td>CAS #</td>
<td>345-78-8</td>
</tr>
<tr>
<td>Molecular formula</td>
<td>C_{10}H_{14}NO_{4}HCl</td>
</tr>
<tr>
<td>Molecular weight</td>
<td>201.69</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>USAN/INN/JAN</th>
<th>Hydrocodone Bitartrate USP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical Name</td>
<td>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)</td>
</tr>
<tr>
<td>CAS #</td>
<td>143-71-5 (anhydrous) 34195-34-1 (Hydrocodone Bitartrate)</td>
</tr>
<tr>
<td>Molecular formula</td>
<td>C_{18}H_{21}N_{03}. C_{4}H_{6}O_{6}. 2 1/2 H_{2}O</td>
</tr>
<tr>
<td>Molecular weight</td>
<td>494.490</td>
</tr>
</tbody>
</table>

**CONSULTS/ CMC RELATED REVIEWS**

<table>
<thead>
<tr>
<th>COMMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Pharm (BA/BE) - Dissolution</td>
</tr>
<tr>
<td>CDRH</td>
</tr>
<tr>
<td>EA</td>
</tr>
</tbody>
</table>
The drug substance site 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.

Consensus is pending. Not necessary

Consult for antimicrobial assessment to be requested.

Depends to stability data for leachables and impurities.

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 . The drug substance is referenced in a DMF which was It 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. The sponsor states that they have not yet identified 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 /day. For the current indication the maximum daily dose of hydrocodone is 20 mg/day for Adults.

- Pseudoephedrine hydrochloride USP is made by . Information is presented in a DMF. This DMF was reviewed for safety during the IND review by Dr. Art Shaw (date 8/14/2008) and previously for and 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][c]. The drug substance is referenced in a DMF [d] 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][c] sucrose and [b][c] 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][c] size while the proposed commercial scale is stated to be [b][c]. 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>
<thead>
<tr>
<th>Table 3.2.P.1-1.</th>
<th>Unit Composition of Oral Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Component</td>
<td>Reference to Quality Standards</td>
</tr>
<tr>
<td>Hydrocodone Bitartrate</td>
<td>USP</td>
</tr>
<tr>
<td>Chlorpheniramine Maleate</td>
<td>USP</td>
</tr>
<tr>
<td>Pseudoephedrine Hydrochloride</td>
<td>USP</td>
</tr>
<tr>
<td>Citric Acid, Anhydrous</td>
<td>USP</td>
</tr>
<tr>
<td>Sodium Citrate</td>
<td>USP</td>
</tr>
<tr>
<td>Sodium Saccharin</td>
<td>USP</td>
</tr>
<tr>
<td>Methylparaben</td>
<td>NF</td>
</tr>
<tr>
<td>Propylparaben</td>
<td>NF</td>
</tr>
<tr>
<td>Sucrose</td>
<td>NF</td>
</tr>
<tr>
<td>Glycerin</td>
<td>USP</td>
</tr>
<tr>
<td>Propylene Glycol</td>
<td>USP</td>
</tr>
<tr>
<td>Grape Flavor</td>
<td>USP</td>
</tr>
<tr>
<td>Water, Purified</td>
<td>USP</td>
</tr>
</tbody>
</table>

**NF** = National Formulary.
Table 3.2.P.1.2. Container Closure for Oral Solution

<table>
<thead>
<tr>
<th>Component</th>
<th>Professional Sample</th>
<th>Commercial Product (480 mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Container</td>
<td>Bottle with a neck finish</td>
<td>(b) (c)</td>
</tr>
<tr>
<td>Closure</td>
<td></td>
<td>(b) (c)</td>
</tr>
</tbody>
</table>

- Drug product is manufactured at by The methods of manufacturing are relatively straight forward.
  The in process tests used are pH, appearance, density, and viscosity.
- The product is filled into Bottle with Neck finish and 16 ounce, white HDPE bottles.
- 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 an 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 that 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 . 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 in the drug Product.** Not applicable.
- **Manufacturing differences between pilot and commercial scales**
  None proposed. The registration stability batches are and the proposed commercial batches are .
- **GMP status of the drug substance/drug product manufacturing sites.**
Note that the sites are sent to the DO for evaluation. (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 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**

- **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.

---

<table>
<thead>
<tr>
<th>Table 2.3.P-16.</th>
<th>Summary of Stability Results for Registration Batch 00658/P08001 (16 oz/480 mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>Acceptance Criterion</td>
</tr>
<tr>
<td>Description</td>
<td></td>
</tr>
<tr>
<td>pH (25 ºC)</td>
<td></td>
</tr>
<tr>
<td>Color</td>
<td></td>
</tr>
<tr>
<td>Viscosity (25 ºC)</td>
<td></td>
</tr>
<tr>
<td>Hydrocodone Bitartrate Assay</td>
<td></td>
</tr>
<tr>
<td>Chlormpheniramine Malate Assay</td>
<td></td>
</tr>
<tr>
<td>Pseudoephedrine Hydrochloride Assay</td>
<td></td>
</tr>
<tr>
<td>Methylparaben Assay</td>
<td></td>
</tr>
<tr>
<td>Propylparaben Assay</td>
<td></td>
</tr>
<tr>
<td>Impurities/Degradants: Specified Known Impurities</td>
<td></td>
</tr>
<tr>
<td>Individual Impurities</td>
<td></td>
</tr>
<tr>
<td>Unspecified Impurities</td>
<td></td>
</tr>
<tr>
<td>Total Impurities</td>
<td></td>
</tr>
</tbody>
</table>
Drug product specifications with batch results are provided in the table below.

<table>
<thead>
<tr>
<th>Component</th>
<th>Commercial Product (480 mL)</th>
<th>Professional Sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>Container:</td>
<td></td>
<td>bottle with a</td>
</tr>
<tr>
<td>Material of Construction</td>
<td></td>
<td>neck finish</td>
</tr>
<tr>
<td>Closure:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Material of Construction:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outer cap</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inner cap</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liner</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DMF</td>
<td>TYPE</td>
<td>HOLDER</td>
</tr>
<tr>
<td>-----</td>
<td>------</td>
<td>--------</td>
</tr>
<tr>
<td>II</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test</td>
<td>Acceptance Criterion</td>
<td>Stability</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>---------------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Appearance/Description</strong></td>
<td>Clear, colorless to light yellow liquid with a grape odor and free from precipitation</td>
<td>Clear, colorless to light yellow liquid with a grape odor and free from precipitation</td>
</tr>
<tr>
<td><strong>Color</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Density</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Viscosity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>pH</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Deliverable Volume</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Identification A:</strong></td>
<td>Hydrocodone Bitartrate, Chlorpheniramine Maleate, and Pseudoephedrine Hydrochloride</td>
<td></td>
</tr>
<tr>
<td><strong>Identification B:</strong></td>
<td>Hydrocodone Bitartrate, Chlorpheniramine Maleate, and Pseudoephedrine Hydrochloride</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Assay:</strong> Hydrocodone Bitartrate (5 mg/5 mL)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chlorpheniramine Maleate (4 mg/5 mL)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pseudoephedrine Hydrochloride (60 mg/5 mL)</td>
<td></td>
</tr>
<tr>
<td>Test</td>
<td>Acceptance Criterion</td>
<td>Analytical Procedure</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>----------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>Methylparaben</td>
<td>(b)(4)</td>
<td>(b)(4)</td>
</tr>
<tr>
<td>Propylparaben</td>
<td>(b)(4)</td>
<td>(b)(4)</td>
</tr>
<tr>
<td>Specified Impurity:</td>
<td>(b)(4)</td>
<td>(b)(4)</td>
</tr>
</tbody>
</table>

| 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 |                      |                      |
| Salmonella species            |                      |                      |
| Escherichia coli              |                      |                      |
| Pseudomonas aeruginosa        |                      |                      |
| Staphylococcus aureus         |                      |                      |
| Packaging                     |                      | Visual               |
| NA                           |                      | NA                   |

<sub>a</sub> = Performed on bulk solution (for release).
<sub>b</sub> = Performed at release only.
<sub>c</sub> = Performed on professional samples (bottles) for release testing only.
<sub>d</sub> = This test will be performed on the stability samples of the commercial batch.

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.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Yes</th>
<th>No</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1  On its face, is the section organized adequately?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2  Is the section indexed and paginated adequately?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3  On its face, is the section legible?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4  Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5  Is a statement provided that all facilities are ready for GMP inspection?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6  Has an environmental assessment report or categorical exclusion been provided?</td>
<td>X</td>
<td></td>
<td>Applicant shows calculations of less than the specified amount listed in the regulations. Consult to be sent</td>
</tr>
<tr>
<td>7  Does the section contain controls for the drug substance?</td>
<td>X</td>
<td></td>
<td>Reference to DMFs and NDA</td>
</tr>
<tr>
<td>8  Does the section contain controls for the drug product?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9  Have stability data and analysis been provided to support the requested expiration date?</td>
<td>X</td>
<td></td>
<td>3 months stability data provided. No shelf life proposed</td>
</tr>
<tr>
<td>10 Has all information requested during the IND phase, and at the pre-NDA meetings been included?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11 Have draft container labels been provided?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 Has the draft package insert been provided?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13 Has an investigational formulations section been provided?</td>
<td>X</td>
<td></td>
<td>Described in the development report</td>
</tr>
<tr>
<td>14 Is there a Methods Validation package?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 Is a separate microbiological section included?</td>
<td>X</td>
<td></td>
<td>Antimicrobial Effectiveness testing to be provided and evaluated</td>
</tr>
<tr>
<td>16 Is a production batch record provided</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Draft CMC Comments for 74 day Letter

1. **Provide references to direct food additive regulations for all the packaging materials (bottles, 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. 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.**
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/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
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Ap  tion: NDA 22439/000
O  e: 570
Priority: 4S
Stamp Date: 07-NOV-2008
PDUFA Date: 07-SEP-2009
Action Goal: 09-JUL-2009

Sponsor: CYPRESS PHARM
Address: 135 INDUSTRIAL BLVD
          MADISON, MS 39110

Brand Name: HYDROCODONE BITARTRATE/CHLORPH

Generic Name: HYDROCODONE, CHLORPHENIRAMINE, PSE

Product Number: 90 (50)
Dosage Form: Ingredient: Potency

FDA Contacts:
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-2006 by E. JOHNSON (HFD-320) 301-796-3334

Establishment:

CFN: 90 (10)  FEl: 90 (10)

DMF No: AADA:
Responsibilities:
DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE PACKAGER
DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER
Profile: 90 (10)
OAI Status: NONE

Last Milestone: OC RECOMMENDATION
Milestone Date: 23-DEC-2008
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Establishment:

CFN: 90 (10)  FEl: 90 (10)

DMF No: 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

Reference ID: 2961030
Drugs Substance Manufacturer
DRUG SUBSTANCE PACKAGER
DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER

Profile:

Last Milestone:
OC RECOMMENDATION

Milestone Date:
05-DEC-2008

Decision:
ACCEPTABLE

Reason:
BASED ON PROFILE

Drugs Substance OTHER Tester
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Profile:

Last Milestone:
OC RECOMMENDATION

Milestone Date:
29-JUN-2009

Decision:
ACCEPTABLE

Reason:
DISTRICT RECOMMENDATION
FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment:  

CFN: (5)(4)  

FEI: (5)(4)  

DMF No:  

Responsibilities:  

DRUG SUBSTANCE MANUFACTURER  

DRUG SUBSTANCE PACKAGER  

DRUG SUBSTANCE RELEASE TESTER  

DRUG SUBSTANCE STABILITY TESTER  

Profile: (5)(4)  

AADA:  

OAI Status:  

NONE  

Last Milestone:  

OC RECOMMENDATION  

Milestone Date:  

31-AUG-2009  

Decision:  

ACCEPTABLE  

Reason:  

DISTRICT RECOMMENDATION  

Establishment:  

CFN: (5)(4)  

FEI: (5)(4)  

DMF No:  

Responsibilities:  

FINISHED DOSAGE OTHER TESTER  

CONTROL TESTING LABORATORY  

OAI Status:  

NONE  

Last Milestone:  

OC RECOMMENDATION  

Milestone Date:  

05-DEC-2003  

Decision:  

ACCEPTABLE  

Reason:  

BASED ON PROFILE