

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**022439Orig1s000**

**OTHER REVIEW(S)**

**PMR: Pediatric Safety Study**  
**Zutripro: NDA 22-439**

PMR/PMC Description: A study to assess the safety of Zutripro (hydrocodone, chlorpheniramine, and pseudoephedrine combination product oral solution) in approximately 400-450 children 6-17 years of age with symptoms of the common cold. The dose used in this study will be based upon the results of the pharmacokinetic study in children ages 6-17 years.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>09/30/2014</u>
	Study/Trial Completion:	<u>12/31/2015</u>
	Final Report Submission:	<u>09/30/2016</u>
	Other:	_____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The product will be approved for the adult population. This PREA-required PMR is for the Applicant to assess the safety of Zutripro and Rezira (hydrocodone, chlorpheniramine, and pseudoephedrine and hydrocodone and pseudoephedrine combination product oral solutions, respectively, in children 6-17 years of age. The dose(s) will be based on the results of a PK study which is also a PREA-required PMR.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The Applicant's hydrocodone, chlorpheniramine, and pseudoephedrine and hydrocodone and pseudoephedrine cough and cold combination product oral solutions, Zutripro and Rezira, respectively, will be approved for adults 18 years of age and older based on previous FDA findings of efficacy and safety. However, the previous determinations of safety lacked sufficient data in children to accurately determine the proper dose and more fully assess the safety of the product, especially the hydrocodone (narcotic) component. Thus, pharmacokinetic and safety trials will be conducted as PREA requirements to help determine the dose and assess safety in children 6-17 years of age.

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3. If the study/clinical trial is a **PMR**, check the applicable regulation.

*If not a PMR, skip to 4.*

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A safety study of the Applicant's hydrocodone, chlorpheniramine, and pseudoephedrine combination product oral solution in approximately 400 children 6-17 years of age with cough and cold symptoms. This study will begin after analysis of the data collected from the pediatric pharmacokinetic study which will be conducted in order to assist in selecting the dose(s) of Zutripro and Rezira for the pediatric population ages 6-17 years.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

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Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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SALLY M SEYMOUR  
06/07/2011

**Pediatric Pharmacokinetic Study**  
**Zutripro: NDA 22-439**

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PMR/PMC Description: A study to assess the pharmacokinetics of each Zutripro drug component (hydrocodone, chlorpheniramine, and pseudoephedrine oral) in approximately 25-35 children ages 6-17 years with symptoms of the common cold. The results of this study will be used to determine the appropriate dose of the combination product to evaluate in a safety study in children ages 6-17 years.

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>09/30/2011</u>
	Study/Trial Completion:	<u>12/31/2013</u>
	Final Report Submission:	<u>06/30/2014</u>
	Other:	_____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The product will be approved for the adult population. This PREA-required PMR is for a pharmacokinetic study of the Applicant's hydrocodone, chlorpheniramine, and pseudoephedrine combination product oral solution in children 6-17 years of age in order to establish doses of Zutripro and the related hydrocodone and pseudoephedrine combination product oral solution (Rezira) for a subsequent pediatric safety study in children 6-17 years of age.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The Applicant's two cough and cold combination products, Zutripro (hydrocodone, chlorpheniramine, and pseudoephedrine oral solution) and Rezira (hydrocodone and pseudoephedrine oral solution) will be approved for adults 18 years of age and older based on previous FDA findings of efficacy and safety. However, the previous determinations of safety lacked sufficient data in children to accurately determine the proper dose and more fully assess the safety of the product, especially the hydrocodone (narcotic) component. Thus, pharmacokinetic and safety trials will be conducted as PREA requirements to help determine the dose and assess safety in children 6-17 years of age. As the Rezira oral solution formulation includes two of the 3 components in the Zutripro product, the same study can be used to assess the PK of the components of both products.

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3. If the study/clinical trial is a **PMR**, check the applicable regulation.

*If not a PMR, skip to 4.*

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

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- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

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- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
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- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Pharmacokinetic study of the Applicant's hydrocodone, chlorpheniramine, and pseudoephedrine combination product oral solution in children 6-17 years of age in order to establish doses of Zutripro and the related hydrocodone and pseudoephedrine combination product oral solution (Rezira) for a subsequent pediatric safety study in children 6-17 years of age.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
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  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
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- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
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**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/  
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SALLY M SEYMOUR  
06/07/2011

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

Date: June 2, 2011

Reviewers: Richard Abate, RPh, MS, Safety Evaluator  
and  
Anne Tobenkin, PharmD, Safety Evaluator  
Division of Medication Error Prevention and Analysis

Through: Carol Holquist, RPh, Director  
Division of Medication Error Prevention and Analysis

Subject: Labeling and Packaging Review

Drug Names and Strengths: Zutripro (Hydrocodone Bitartrate, Chlorpheniramine Maleate, and Pseudoephedrine Hydrochloride) Oral Solution, 5 mg/4 mg/60 mg per 5 mL  
  
Rezira (Hydrocodone Bitartrate and Pseudoephedrine Hydrochloride) Oral Solution, 5 mg/60 mg per 5 mL

Application Type/Numbers: NDA 022439 (Zutripro)  
NDA 022442 (Rezira)

Applicant/sponsor: Cypress Pharmaceuticals

OSE RCM #: 2011-328-1 and 2011-379-1

## **1 INTRODUCTION**

This review evaluates the revised fill volume of the professional samples from (b)(4) to 5 mL for Zutripro (Hydrocodone Bitartrate, Chlorpheniramine Maleate, and Pseudoephedrine Hydrochloride) Oral Solution for NDA 022439 and Rezira (Hydrocodone Bitartrate and Pseudoephedrine Hydrochloride) Oral Solution for NDA 022442. This Applicant submitted the revision pursuant to a request from the Division of Pulmonary, Allergy and Rheumatology Products on May 25, 2011 following DMEPA's recommendation not to approve the (b)(4) size for safety reasons (see OSE reviews #2011-328 dated May 2, 2011 and OSE review # 2011-37 dated May 24, 2011 for Rezira (Hydrocodone Bitartrate and Pseudoephedrine Hydrochloride) Oral Solution.)

## **2 DISCUSSION AND CONCLUSIONS**

Following receipt of DMEPA's recommendations, the Applicant submitted revised container labels and carton labeling for both Zutripro (NDA 022439) and Rezira (NDA 022442) with revised fill volumes for the professional samples of each product to 5 mL or one dose. Therefore, DMEPA agrees with the approval of the professional samples with a 5 mL fill volume as presented in the May 27, 2011 submissions for Zutripro (NDA 022439) and Rezira (NDA 022442). Additionally, DMEPA communicated the acceptability of the revised container labels and carton labeling via e-mail to DPARP on Tuesday, May 31, 2011.

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/s/  
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RICHARD A ABATE  
06/02/2011

CAROL A HOLQUIST  
06/02/2011

505(b)(2) ASSESSMENT

Application Information		
NDA # 22-439	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Zutripro® Established/Proper Name: hydrocodone, chlorpheniramine, pseudoephedrine Dosage Form: oral solution Strengths: 5mg/4mg/60mg/ in 5 ml		
Applicant: Cypress Pharmaceutical, Inc.		
Date of Receipt: December 8, 2010		
PDUFA Goal Date: June 8, 2011		Action Goal Date (if different):
Proposed Indication(s): 1. Relief of cough and nasal congestion associated with common cold 2. Relief of symptoms including nasal congestion associated with upper respiratory allergies		

**GENERAL INFORMATION**

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES  NO

*If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*



**INFORMATION PROVIDED VIA RELIANCE  
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
NDA 05-213 <b>Hycodan</b>	Label Sections 1.0, 4.0, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 6.1, 7.1, 7.2, 8.1, 8.2, 8.3, 8.4, 8.6, 8.7, 8.8, 9.1, 9.2, 9.3, 10.1, 10.2, 12.1,
NDA 19-111 ** <b>Tussionex</b> Extended Release Suspension	Label Sections 5.4, 6.1, 8.5, 10.1, 12.1,
NDA 21-369 ** <b>Codeprex</b> Extended-Release Suspension	Label Sections 6.1, 7.3, 8.1, 8.3, 8.4, 10.1, 10.2, 13.1
<b>21 CFR 201.57(c)(3)</b> Specific requirements on content and format of labeling . . .	Label Section 8.1
<b>21 CFR 341.72</b> Labeling of antihistamine drug products	Label Sections 1.0, 2.1, 2.2, 5.5, 17.1
<b>21 CFR 341.80</b> Labeling of nasal decongestant drug products	Label Sections 1.0, 2.1, 2.2, 5.1, 5.6, 7.2, 17.1
Mosby Drug Reference **	Label Sections 12.1

\*each source of information should be listed on separate rows

\*\* Although the applicant cited reliance on this information in the cover letter and annotated labeling submitted in their original application, the review division has determined that reliance on this information is not necessary for approval.

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

**This application relies on a BA/BE study of the proposed product to the referenced products. No clinical studies for safety and efficacy were required to support this application.**

**RELIANCE ON PUBLISHED LITERATURE**

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES  NO   
 If "NO," proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES  NO   
 If "NO", proceed to question #5.  
 If "YES", list the listed drug(s) identified by name and answer question #4(c).

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES  NO

**RELIANCE ON LISTED DRUG(S)**

*Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.*

- 5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES  NO   
 If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Hycodan	NDA 05213	Y
Tussionex *	NDA 19111	Y*
Tavist Allergy/Sinus *	NDA 21082	Y*
Advil Allergy Sinus Caplets*	NDA 21441	Y*

**\*Although the applicant cited reliance on this information in the cover letter and annotated labeling submitted in their original application, the review division has determined that reliance on this information is not necessary for approval**

*Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?  
N/A  YES  NO

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".*

*If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES  NO   
*If "YES", please list which drug(s)*

Name of drug(s) approved in a 505(b)(2) application: **Tavist Allergy/Sinus**

- b) Approved by the DESI process?

YES  NO   
*If "YES", please list which drug(s).*

Name of drug(s) approved via the DESI process: **Hycodan**

- c) Described in a monograph?

YES  NO   
*If "YES", please list which drug(s).*

Name of drug(s) described in a monograph:

**Chlorpheniramine, 21CFR §341.12**  
**Pseudoephedrine, 21 CFR §341.20**

- d) Discontinued from marketing?

YES  NO   
*If "YES", please list which drug(s) and answer question d) i. below.*  
*If "NO", proceed to question #9.*

Name of drug(s) discontinued from marketing: **Hycodan**

- i) Were the products discontinued for reasons related to safety or effectiveness?  
YES  NO

*(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If*

*a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)*

- 9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsule to solution”).

**This application provide for a new combination drug product.**

*The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.*

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

- 10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; **and** (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES  NO

*If “**NO**” to (a) proceed to question #11.*

*If “**YES**” to (a), answer (b) and (c) then proceed to question #12.*

- (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES  NO

- (c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES  NO

*If “**YES**” to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*

*If “**NO**” or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all*

of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

*Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES  NO

If "NO", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES  NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES  NO

If "YES" and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

#### PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed  proceed to question #14

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES  NO

*If "NO", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

- 14) Which of the following patent certifications does the application contain? (*Check all that apply and identify the patents to which each type of certification was made, as appropriate.*)

No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

21 CFR 314.50(i)(1)(ii): No relevant patents.

21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES  NO

*If "NO", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES  NO

*If "NO", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

*Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES  NO  Patent owner(s) consent(s) to an immediate effective date of approval

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/s/  
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PHILANTHA M BOWEN  
06/02/2011

# **REGULATORY PROJECT MANAGER PLR FORMAT LABELING REVIEW**

**Application:** NDA 22439/000  
**Name of Drug:** Zutripro (hydrocodone/CHM/PSE)

**Applicant:** Cypress Pharmaceuticals Inc.  
**Review Date:** May 3, 2011

## **Labeling Reviewed**

**Submission Date:** December 8, 2010

**Receipt Date:** December 8, 2010

## **Background and Summary Description**

On December 8, 2010, Cypress Pharmaceuticals resubmitted a 505(b)(2) New Drug Application for hydrocodone, chlorpheniramine, and pseudoephedrine for relief of cough and nasal congestion associated with common cold; and relief of symptoms including nasal congestion associated with upper respiratory allergies.

The proposed labeling was provided in SPL, including electronic carton and container labels.

OSE and DDMAC will be consulted regarding the labeling, as appropriate to their discipline, for recommendations regarding the proposed content.

## **Review**

The submitted labeling was reviewed in accordance with the labeling requirements listed in the “Selected Requirements for Prescribing Information (SRPI)” section of this review. Labeling deficiencies are identified in this section with an “X” in the checkbox next to the labeling requirement.

- Replace “TRADENAME” with the accepted name “ZUTRIPRO” for the product throughout the package insert.
- Change Initial U.S. Approval date to 2011

## **Conclusions/Recommendations**

All labeling deficiencies identified in the SRPI section of this review will be conveyed to the applicant in the Division’s initial request for labeling revisions. The applicant will be asked to resubmit labeling that addresses all identified labeling deficiencies. The resubmitted labeling will be used for further labeling discussions.

## Selected Requirements for Prescribing Information (SRPI)

### Highlights (HL)

- **General comments**

- HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.
- HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission.
- There is no redundancy of information.
- If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)
- A horizontal line must separate the HL and Table of Contents (TOC).
- All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and **bold** type.
- Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
- Section headings are presented in the following order:

• <b>Highlights Limitation Statement</b> (required statement)
• <b>Drug names, dosage form, route of administration, and controlled substance symbol, if applicable</b> (required information)
• <b>Initial U.S. Approval</b> (required information)
• <b>Boxed Warning</b> (if applicable)
• <b>Recent Major Changes</b> (for a supplement)
• <b>Indications and Usage</b> (required information)
• <b>Dosage and Administration</b> (required information)
• <b>Dosage Forms and Strengths</b> (required information)
• <b>Contraindications</b> (required heading – if no contraindications are known, it must state “None”)
• <b>Warnings and Precautions</b> (required information)
• <b>Adverse Reactions</b> (required AR contact reporting statement)
• <b>Drug Interactions</b> (optional heading)
• <b>Use in Specific Populations</b> (optional heading)
• <b>Patient Counseling Information Statement</b> (required statement)
• <b>Revision Date</b> (required information)

- **Highlights Limitation Statement**
  - Must be placed at the beginning of HL, **bolded**, and read as follows: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”
  
- **Product Title**
  - Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.
  
- **Initial U.S. Approval**
  - The verbatim statement “Initial U.S. Approval” followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.
  
- **Boxed Warning**
  - All text in the boxed warning is **bolded**.
  - Summary of the warning must not exceed a length of 20 lines.
  - Requires a heading in UPPER-CASE, **bolded** letters containing the word “**WARNING**” and other words to identify the subject of the warning (e.g., “**WARNING: LIFE-THREATENING ADVERSE REACTIONS**”).
  - Must have the verbatim statement “*See full prescribing information for complete boxed warning.*” If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary.
  
- **Recent Major Changes (RMC)**
  - Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
  - The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, “Dosage and Administration, Coronary Stenting (2.2) --- 2/2010.”
  - For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line (“margin mark”) on the left edge.
  - A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.
  - Removal of a section or subsection should be noted. For example, “Dosage and Administration, Coronary Stenting (2.2) --- removal 2/2010.”

- **Indications and Usage**

- If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product) is a (name of class) indicated for (indication(s)].” Identify the established pharmacologic class for the drug at:

<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm>.

- **Contraindications**

- This section must be included in HL and cannot be omitted. If there are no contraindications, state “None.”
- All contraindications listed in the FPI must also be listed in HL.
- List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.
- For drugs with a pregnancy Category X, state “Pregnancy” and reference Contraindications section (4) in the FPI.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).
- For drug products other than vaccines, the verbatim **bolded** statement, “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s phone number) or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch)**” must be present. Only include toll-free numbers.

- **Patient Counseling Information Statement**

- Must include the verbatim statement: “**See 17 for Patient Counseling Information**” or if the product has FDA-approved patient labeling: “**See 17 for Patient Counseling Information and (insert either “FDA-approved patient labeling” or “Medication Guide”)**”.

- **Revision Date**

- A placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year,” must appear at the end of HL. The revision date is the month/year of application or supplement approval.

**Contents: Table of Contents (TOC)**

- The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at

the beginning in UPPER CASE and **bold** type.

- The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.
- All section headings must be in **bold** type, and subsection headings must be indented and not bolded.
- When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:
  - 8.1 Pregnancy
  - 8.3 Nursing Mothers (not 8.2)
  - 8.4 Pediatric Use (not 8.3)
  - 8.5 Geriatric Use (not 8.4)
- If a section or subsection is omitted from the FPI and TOC, the heading “**Full Prescribing Information: Contents**” must be followed by an asterisk and the following statement must appear at the end of TOC: “\*Sections or subsections omitted from the Full Prescribing Information are not listed.”

### **Full Prescribing Information (FPI)**

- **General Format**

- A horizontal line must separate the TOC and FPI.
- The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.
- The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).

- **Boxed Warning**

- Must have a heading, in UPPER CASE, **bold** type, containing the word “**WARNING**” and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the text.
- Must include a brief, concise summary of critical information and cross-reference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).

- **Contraindications**

- For Pregnancy Category X drugs, list pregnancy as a contraindication.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(c)(7) should be included in

labeling. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided.

- For the “Clinical Trials Experience” subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

- For the “Postmarketing Experience” subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

- **Use in Specific Populations**

- Subsections 8.4 Pediatric Use and 8.5 Geriatric Use are required and cannot be omitted.

- **Patient Counseling Information**

- This section is required and cannot be omitted.
- Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement “See FDA-approved patient labeling (insert type of patient labeling).” should appear at the beginning of Section 17 for prominence. For example:
  - “See FDA-approved patient labeling (Medication Guide)”
  - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
  - “See FDA-approved patient labeling (Patient Information)”
  - “See FDA-approved patient labeling (Instructions for Use)”
  - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

*See Appended Electronic Signature*

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Regulatory Project Manager

Date

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Chief, Project Management Staff

Date

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/s/  
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PHILANTHA M BOWEN  
05/05/2011

SANDRA L BARNES  
05/05/2011

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications**

**\*\*\*Pre-decisional Agency Information\*\*\***

## Memorandum

**Date:** May 4, 2011

**To:** Philantha Bowen, Regulatory Project Manager  
Division of Pulmonary, Allergy, and Rheumatology Products  
(DPARP)

**From:** Roberta Szydlo, Regulatory Review Officer  
Division of Drug Marketing, Advertising, and Communications  
(DDMAC)

**CC:** Lisa Hubbard, Professional Group Leader  
Robyn Tyler, Acting DTC Group Leader  
Matthew Falter, Regulatory Review Officer  
Olga Salis, Regulatory Health Project Manager  
Michael Wade, Regulatory Health Project Manager  
(DDMAC)

**Subject:** NDA # 022439  
DDMAC labeling comments for ZUTIPRO™ (hydrocodone bitartrate,  
chlorpheniramine maleate, and pseudoephedrine hydrochloride)  
Oral Solution (Zutipro)

---

DDMAC has reviewed the revised proposed prescribing information (PI) and the proposed carton/container labeling for Zutipro submitted for consult on January 25, 2011.

DDMAC's comments on the PI are based on the proposed draft marked-up labeling titled "NDA 22439 – FDA Proposed Label (4-27-11).doc" that was sent via email from DPARP to DDMAC on April 27, 2011. DDMAC's comments on the PI are provided directly in the marked-up document attached (see below).

DDMAC has reviewed the proposed carton/container labeling located in the EDR at: <\\cdsesub5\EV\SPROD\NDA022439\0025\m1\us\114-labeling\114b-final-label\final-carton-contain.pdf>. We have no comments at this time on the proposed carton/container labeling.

Thank you for the opportunity to comment on these proposed materials.

If you have any questions, please contact Roberta Szydlo at (301) 796-5389 or [roberta.szydlo@fda.hhs.gov](mailto:roberta.szydlo@fda.hhs.gov).

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ROBERTA T SZYDLO  
05/04/2011

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

**Label and Labeling Review**

Date: May 2, 2011

Reviewer(s): Richard Abate, RPh, MS, Safety Evaluator  
Division of Medication Error Prevention and Analysis

Team Leader Melina Griffis, RPh, Team Leader  
Division of Medication Error Prevention and Analysis

Division Director Carol Holquist, RPh, Director  
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Zutripro (Hydrocodone Bitartrate, Chlorpheniramine Maleate, and Pseudoephedrine Hydrochloride) Oral Solution, 5 mg/4 mg/60 mg per 5 mL

Application Type/Number: NDA 022439

Applicant/sponsor: Cypress Pharmaceuticals

OSE RCM #: 2011-328

## 1 INTRODUCTION

This review summarizes the Division of Medication Error Prevention and Analysis (DMEPA) evaluation of the proposed container labels and carton and insert labeling for Zutripro (Hydrocodone Bitartrate, Chlorpheniramine Maleate and Pseudoephedrine HCl) Oral Solution. DMEPA evaluates the labels and labeling for vulnerabilities to confusion that may lead to medication errors.

### 1.1 REGULATORY HISTORY

DMEPA previously reviewed container labels and carton and insert labeling in OSE review # 2009-2441 dated May 7, 2010. Our comments were forwarded to the Applicant, but the NDA received a Complete Response June 11, 2010.

### 1.2 PRODUCT INFORMATION

Zutripro is an oral solution indicated for the treatment of cough and nasal congestion associated with the common cold and the relief of symptoms associated with upper respiratory allergies. Zutripro is indicated for use in adults 18 years of age and older. The dose is 5 mL by mouth every four to six hours, not to exceed four doses (20 mL) in 24 hours. Zutripro is available in bottles containing 480 mL (16 fluid ounces) which are stored at room temperature.

## 2 METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis<sup>1</sup> and human factor principles, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted April 20, 2011
- Carton Labeling submitted April 20, 2011
- Insert Labeling submitted December 8, 2010

## 3 DISCUSSION OF DEFICIENCIES IDENTIFIED

DMEPA identified the following deficiencies related to Zutripro.

### 3.1 PRODUCT DESIGN

The professional samples are packaged as (b) (4) unit of use containers. (b) (4)

### 3.2 CONTAINER LABELS, CARTON LABELING AND INSERT LABELING

No deficiencies identified. We note the proposed labels and labeling include the previously requested revisions per OSE review # 2009-2441.

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<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

#### 4 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that the proposed commercial-size container label and insert labeling are acceptable. However, the fill volume of the professional sample introduces vulnerability that can lead to medication errors (b) (4)

. DMEPA recommends Zutripro professional sample not be approved as proposed. We recommend the following:

- A. Limit the fill volume of the Zutripro professional sample presentation to a 5 mL to minimize the risk of accidental overdose with this product.

If you have further questions or need clarifications, please contact Nichelle Rashid, project manager, at 301-796-3904.

## APPENDICES

### Appendix A: Container Labels – 480 mL

**USUAL DOSAGE:** See Package Insert for Complete Dosage Recommendations. Dispense in a tight, light-resistant container with a child-resistant closure.

**WARNING: KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.**

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature].

Temper evident by foil seal under cap. Do not use if foil seal is broken or missing.

Manufactured for: Hawthorn Pharmaceuticals, Inc., Madison, MS 38110  
HL194 04/11

Lot No:  
Exp. Date:

NDC 63717-876-16

**ZUTRIPRO<sup>®</sup> OTC**  
(Hydrocodone Bitartrate, Chlorpheniramine Maleate and Pseudoephedrine HCl) Oral Solution

**5 mg/4 mg/60 mg per 5 mL**

**Contains:**  
Hydrocodone Bitartrate \_\_\_\_\_ 5 mg/5 mL  
**WARNING: May be habit forming.**  
Chlorpheniramine Maleate \_\_\_\_\_ 4 mg/5 mL  
Pseudoephedrine Hydrochloride \_\_\_\_\_ 60 mg/5 mL

**Rx Only**

**HAWTHORN**  
PHARMACEUTICALS, INC.

**16 fl oz (480 mL)**

### Appendix B: Professional Sample Container Label – (b) (4)



**Appendix D:** Professional Sample Carton Labeling - 12 x (b) (4)



(b) (4)

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/s/  
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RICHARD A ABATE  
05/02/2011

MELINA N GRIFFIS  
05/03/2011

CAROL A HOLQUIST  
05/03/2011

MEMORANDUM

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

DATE: April 14, 2011

TO: Badrul A. Chowdhury, M.D.  
Director, Division of Pulmonary, Allergy and  
Rheumatology Products  
Office of Drug Evaluation

Chandrasah Sahajwalla, Ph.D.  
Director, Division of Clinical Pharmacology-2  
Office of Clinical Pharmacology

FROM: Sripal R. Mada, Ph.D.  
GLP and Bioequivalence Branch  
Division of Scientific Investigations

THROUGH: Martin K. Yau, Ph.D.  
Acting Team Leader - Bioequivalence  
GLP and Bioequivalence Branch  
Division of Scientific Investigations

SUBJECT: Review of EIR Covering NDA 22-439, (b)(4)  
(Hydrocodone / Chlorpheniramine / Pseudoephedrine)  
Oral Solution, 5 mg / 4 mg / 60 mg per 5 mL, from  
Cypress Pharmaceutical, Inc.

At the request of the Division of Pulmonary, Allergy and Rheumatology Products (DPARP), the Division of Scientific Investigations (DSI) conducted inspections of clinical and analytical portions of the following study:

**11058503**: "A Relative Bioavailability and Drug Interaction Study of Hydrocodone Bitartrate / Chlorpheniramine Maleate / Pseudoephedrine HCl, 5 mg/4 mg / 60 mg per 5 mL Oral Solution, CIII (Manufactured by: (b)(4) Manufactured for: Cypress Pharmaceutical, Inc.) Compared to Hydrocodone Bitartrate and Homatropine Methyl bromide Syrup, 5mg / 1.5 mg per 5 ml (Manufactured by Hi-Tech Pharmacal Co., Inc.), Pseudoephedrine HCl Oral Solution, 60 mg per 5 ml (Manufactured by: (b)(4) Manufactured for: Cypress Pharmaceutical, Inc.) and Chlorpheniramine Maleate

Page 2 - NDA 22-439, (b)(4) (Hydrocodone / Chlorpheniramine / Pseudoephedrine) Oral Solution, 5 mg / 4 mg / 60 mg per 5 mL

Oral Solution, 4 mg per 5 ml (Manufactured by: (b)(4) Manufactured for: Cypress Pharmaceutical, Inc.) in Healthy Volunteers under Fasted Conditions"

**CLINICAL INSPECTION:**

The inspection of clinical portion was conducted at **Novum Pharmaceutical Research Services, Houston, TX**. Following the inspection (February 15-28, 2011), No Form FDA-483 was issued.

**ANALYTICAL INSPECTION:**

The inspection of analytical portion was conducted at (b)(4). Following the inspection at (b)(4) (March 7-11, 2011), Form FDA-483 was issued (**Attachment SRM1**). The firm's response, dated March 25, 2011, was received on March 28, 2011 (**Attachment SRM2**).

Our evaluation of the Form FDA-483 observations and the firm's response follows:

**1. The audit trail feature was turned off during analysis of pseudoephedrine plasma samples in run # 3, 4, 5, 6, 7, 8, 9, 35, 36, 37, 38, 39, 40, 41, 42, 43 and 44.**

In their response to Form FDA-483, (b)(4) said 27 analytical runs (run # 1, 2 and 10-34) were tested on System-K and 26 runs (run # 3-9 and 35-53) on System-N. On October 5, 2010, (b)(4) discovered that AB Sciex Analyst software audit trail for pseudoephedrine analysis on System-N had defaulted to incorrect audit trail setting, resulting in incomplete audit trail for the first 17 runs performed on System-N. This discrepancy resulted in incomplete audit trail and not the full audit trails.

(b)(4) tried the remedial actions to obtain the full audit trails for the integration of the data for the 17 affected runs. So, (b)(4) created new project "Pseudoephedrine Clinical Trials" on System-N with fully functional audit trail. Analyst raw data files from 17 affected runs were duplicated from the original project folder "Pseudoephedrine" into the "Pseudoephedrine Clinical Trials" project folder. Each run was integrated in the new project folder under full audit trail.

Page 3 - NDA 22-439, (b)(4) (Hydrocodone / Chlorpheniramine / Pseudoephedrine) Oral Solution, 5 mg / 4 mg / 60 mg per 5 mL

(b)(4) confirmed that the pseudoephedrine data generated from the original (without full audit trail) and second (with full audit trail) integrations were identical.

DSI finds this response to Form FDA-483 adequate.

**2. Failure to conduct sample processing steps for chlorpheniramine under the protection of yellow light as well as failure to store samples in amber colored vials.**

Specifically, according to the product certificate of analysis and stock solution preparation sheets, chlorpheniramine is a light sensitive compound and should be stored under dark condition. However, there is no access of yellow lights in the processing area and all the sample processing events were conducted under white light.

In their response to Form FDA-483, (b)(4) conducted a new experiment. (b)(4) conducted this experiment by storing high and low QCs with and without wrapping aluminum foil for 48 hours at room temperature, 4°C and -20°C. A freshly prepared calibration curve was injected into the LC-MS/MS along with the QC samples.

The results (see **Attachment SRM2**) confirmed that light protection for the study samples during storage and analysis is not essential.

DSI finds this response to Form FDA-483 adequate.

**3. Failure to conduct hydrocodone long term freezer stability experiment at -80°C for hydrocodone containing homatropine.**

Specifically, in one arm of the study # 11058503, subjects were treated with both hydrocodone and homatropine, and analysis was conducted to determine the plasma concentrations of hydrocodone. However, freezer stability of hydrocodone in the presence of homatropine was not established.

In their response to Form FDA-483, (b)(4) said due to the delay in obtaining the homatropine reference standard, the preparation of hydrocodone stability samples in the presence of homatropine could not commence until mid September 2010. However, long term stability experiment was completed by the end of the FDA inspection and results were provided in the Form FDA-483 response (see **Attachment SRM2**). (b)(4) demonstrated stability of

Page 4 - NDA 22-439, (b)(4) (Hydrocodone / Chlorpheniramine / Pseudoephedrine) Oral Solution, 5 mg / 4 mg / 60 mg per 5 mL

hydrocodone in the presence of homatropine for 173 days when stored at  $-80\pm 10^{\circ}\text{C}$ .

DSI finds this response to Form FDA-483 adequate.

**4. Failure to document all aspects of the sample processing events properly during the study conduct.**

Specifically,

(a) Long term stability at  $-80^{\circ}\text{C}$  for hydrocodone indicated that QC samples were prepared and stored initially at  $-20^{\circ}\text{C}$  freezers for 3 days before transferring to  $-80^{\circ}\text{C}$  freezers. However, no documentation in the source records indicating that samples from that lot number were transferred, as the link using lot numbers were not documented.

(b) Sample processing events (stock solution sample dilutions) for dilution integrity study for hydrocodone were not documented properly.

(c) Sample storage details for the 3rd cycle of freeze/thaw study were not documented for hydrocodone during validation.

(d) Per the protocol, plasma samples should be stored in freezers at temperature range  $-80\pm 10^{\circ}\text{C}$ . However, bioanalytical report states plasma samples were stored in freezer range  $-60$  to  $-90^{\circ}\text{C}$ .

(e) Samples for hydrocodone study in run # 15 were re-injected during production run. However, re-injection details were not documented properly in the source documents.

In their response to Form FDA-483, (b)(4) provided adequate explanation for their failure to properly document the above items cited under Form FDA-483 observations. (b)(4) also indicated they will re-train the staff to ensure all the source data are maintained and submitted.

DSI finds this response to Form FDA-483 adequate, and that this observation will not likely to have significant impact on study outcome.

**Conclusion:**

Following evaluation of all Form FDA-483 items and written response from (b)(4), DSI recommends that the clinical and analytical data generated in study 11058503 be accepted for the review.

Page 5 - NDA 22-439, (b)(4) (Hydrocodone / Chlorpheniramine / Pseudoephedrine) Oral Solution, 5 mg / 4 mg / 60 mg per 5 mL

After you have reviewed this transmittal memo, please append it to the original NDA submission.

Sripal R. Mada, Ph.D.  
Bioequivalence, GLP and Bioequivalence Branch, DSI

**Final Classifications:**

**NAI - Novum Pharmaceutical Research Services, Houston, TX**  
FEI: 3003737189

**VAI - (b)(4)**  
FEI: (b)(4)

CC:  
DSI/Ball  
DSI/GLPBB/Mada/Dejernett/Yau/Haidar/CF  
OCP/DCP2/Shang/Xu/Doddapaneni/Sahajwalla  
ODE2/DPARP/Chowdhury/Bowen  
HFR-SW1580/Turner  
HFR-CE850/Edwin  
Draft: SRM 04/08/2011  
Edit: MKY 04/14/2011  
DSI: 6170; O:\Bioequiv\EIRCover\22439cyp.rez.doc  
FACTS: 1253517

Email: DSI/CDER DSI PM TRACK

**ATTACHMENT: 1**

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/s/  
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SRIPAL R MADA

04/14/2011

Original documents are available in the DSI file.

MARTIN K YAU

04/14/2011

**DSI CONSULT**  
**Request for Biopharmaceutical Inspections**

**DATE:** December 23, 2010

**TO:** Associate Director for Bioequivalence  
 Division of Scientific Investigations, HFD-48

**FROM:** Philantha M. Bowen, MPH, RN, Senior Regulatory Project Manager, Division of  
 Pulmonary, Allergy, and Rheumatology Products, HFD-570

**SUBJECT: Request for Biopharmaceutical Inspections**  
 NDA 22439  
 Hydrocodone, Chlorpheniramine, and Pseudoephedrine Oral Solution

**Study/Site Identification:**

The following studies/sites pivotal to approval (OR, raise question regarding the quality or integrity of the data submitted and) have been identified for inspection:

Study #	Clinical Site (name, address, phone, fax, contact person, if available)	Analytical Site (name, address, phone, fax, contact person, if available)
<b>11058503</b>	Kunjeelal Chandrakar, M.D. Novum Pharmaceutical Research Services Wilcrest Green Office Park 3320 Walnut Bend Lane Houston, TX 77042-4712	(b) (4)

**International Inspections:**

**(Please note: International inspections require sign-off by the ORM Division Director or DPE Division Director.)**

We have requested an international inspection because:

\_\_\_\_\_ There is a lack of domestic data that solely supports approval;

\_\_\_\_\_ Other (please explain):

**Goal Date for Completion:**

We request that the inspections be conducted and the Inspection Summary Results be provided by March 15, 2011. We intend to issue an action letter on this application by **June 8, 2011**.

Should you require any additional information, please contact Philantha M. Bowen, Sr. Regulatory Project Manager, at 301-796-2466.

Concurrence: (Optional)

Yun Xu, M.D., Ph.D., Clinical Pharmacology Team Leader (Acting)

Elizabeth Shang, Ph.D., Clinical Pharmacology Reviewer

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/s/  
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PHILANTHA M BOWEN  
12/23/2010

**MEMORANDUM**

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

**DATE:** July 2, 2010

**TO:** NDA 22439 and NDA 22442

**THROUGH:** Prasad Peri, Ph.D., Acting Branch Chief, Branch 8, Division of New Drug Quality Assessment III/Office of New Drug Quality Assessment

**FROM:** Carol Hill

**SUBJECT:** Clarification Request

The following request for clarification of comment 5 in the Complete Response Letter dated, June 11, 2010 was received, via e-mail correspondence, on June 18, 2010, from Janice DeLeon, Director of Product Development for Cypress Pharmaceuticals:

Could you please check with the reviewing chemist to confirm the correct impurity that they want us to monitor on commercial batches?

The Complete Response Letter requests that we include (b) (4) in the drug product commercial specification:

5. (b) (4)

These impurities should be reported when they are at or above the ICH reporting threshold of 0.10%

(b) (4)

As you can see on the attached excerpt from NDA 022439, our specification includes (b) (4)

Please confirm that the impurity to add to the commercial specification is [REDACTED] <sup>(b) (4)</sup>.

*Our response to Cypress via email on June 18, 2010, clarified that in comment 5 [REDACTED] <sup>(b) (4)</sup>*

[REDACTED]

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22439

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ORIG-1

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CYPRESS  
PHARMACEUTICA  
L INC

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(b) (4) (HYDROCODONE  
BITARTRATE/CHLORPH

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/s/  
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CAROL F HILL  
07/02/2010

# **REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)**

## **Division of Pulmonary and Allergy Products**

**Application Number:** NDA 22-439/S-000

**Name of Drug:** (b)(4) (hydrocodone, chlorpheniramine, and pseudoephedrine) oral solution

**Applicant:** Cypress Pharmaceuticals

### **Material Reviewed:**

**Submission Date(s):** December 10, 2009 and May 17, 2010

**Receipt Date(s):** December 11, 2009 and May 17, 2010

**Submission Date of Structure Product Labeling (SPL):** December 10, 2009

**Type of Labeling Reviewed:** Package Insert, Carton, and Container

### **Background and Summary**

On December 10, 2009, Cypress Pharmaceuticals resubmitted a New Drug Application for (b)(4) for relief of cough and nasal congestion associated with common cold and for the relief of symptoms including nasal congestion associated with upper respiratory allergies.

The proposed labeling text for (b)(4) was provided in SPL and draft labeling text, including carton and container labels.

OSE and DDMAC were consulted regarding the proposed labeling for recommendations regarding the content.

### **Review**

The proposed labeling was reviewed using the Label Review Tool provided by SEALD. I identified the following comments pertaining to the format of the Full Prescribing Information-Table of Contents and Details sections of the product label:

### Full Prescribing Information - Table of Contents:

- A horizontal line must be located between the Table of Contents and the FPI.

### Full Prescribing Information - Details :

- Cross-references are embedded in the text in the FPI, thus the use of italics is recommended. Do not use all capital letters. References should appear as [*see Warnings and Precautions (5.4)*]

- ADVERSE REACTIONS

The clinical trials and the postmarketing experience statements or an appropriate modification should precede the presentation of adverse reactions. Choose one or both statements as appropriate to identify the source of the adverse reactions.

- PATIENT COUNSELING INFORMATION

The reference [*See FDA-Approved Patient Labeling*] should appear at the beginning of this section.

The Division sent a facsimile dated May 5, 2010, to Cypress containing a marked-up version of the PI illustrating recommended labeling revisions, including the consult recommendations and the format comments listed above. Also on May 12, 2010, additional labeling comments were sent to Cypress via facsimile.

Cypress submitted a response dated May 17, 2010. The amendment contained draft labeling text for the package insert and carton and container labels. All changes were made to the proposed package insert and carton and container labels as recommended in the facsimiles with the exception of the request to move the contents statement to the side panel on the 16 fl oz bottle label. Cypress explained that the right panel on the label proof appears to be blank and available for text; however, it is actually a clear panel that shows the first page of the package insert under the clear panel. The format informs the pharmacist that the package insert is available under the wrapping bottle label. Cypress has adjusted the principal display panel to maximize the separation and clarity of the text.

### **Recommendations**

The recommended action for this application is a complete response based on the deficiencies identified in the Division of Scientific Investigations bioequivalence establishment inspection reports dated May 5 and 25, 2010.

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Carol Hill for  
Philantha M. Bowen  
Regulatory Project Manager  
CDER, OND, ODE II

Supervisory Comment/Concurrence:

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Sandy Barnes  
Chief, Project Management Staff  
CDER, OND, ODE II

Drafted: Bowen/February 24, 2010  
Hill/June 4, 2010  
Initialed: Barnes/June 9, 2010  
Finalized: Hill for Bowen/June 10, 2010

Filename: N22-442 (000) Resub I PLR Review  
**CSO LABELING REVIEW OF PLR FORMAT**

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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/s/

CAROL F HILL  
06/10/2010

SANDRA L BARNES  
06/18/2010

## MEMORANDUM

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

**TO:** NDA 022439  
NDA 022442

**FROM:** Kim Quaintance  
Associate Director for Regulatory Affairs  
Office of New Drugs

**SUBJECT:** Addendum to 505(b)(2) Assessments

This memorandum seeks to further clarify the listed drug relied upon to support approval of the proposed 505(b)(2) applications.

The applicant for NDA 022439 and NDA 022442, Cypress Pharmaceuticals, Inc., (Cypress) cited reliance on FDA's finding of safety and effectiveness for Hycodan Syrup (NDA 005213, applicant: Endo Pharmaceuticals), Tussionex Extended Release Suspension (NDA 019111, applicant: UCB Inc), and Codeprex Extended Release Suspension (NDA 021369, applicant: UCB Inc) to support approval of its 505(b)(2) application in their original application received November 7, 2008 and November 10, 2008, respectively. In the applicant's responses to our Complete Response letters, Cypress added another listed drug relied upon to support approval of its 505(b)(2) applications: Hi-Tech Syrup (ANDA 040613, applicant: Hi Tech Pharmacal Co, Inc.) but did not indicate that it no longer sought to rely on Hycodan Syrup.

Hycodan Syrup is listed in the "Discontinued" section of the Orange Book, but was not withdrawn from sale for reasons of safety or effectiveness. Cypress conducted bioequivalence trials with Hycodan Syrup before it was discontinued.

As outlined in the (b)(2) assessments, while the applicant cited reliance on Tussionex and Codeprex, the review division determined that reliance on these two listed drugs was not necessary for approval of these (b)(2) applications.

Although it was approved in an ANDA, Hi-Tech Syrup is designated in the Orange Book as a reference listed drug (RLD) because Hycodan Syrup, the previous RLD, has been discontinued. Given that only a listed drug approved for safety and effectiveness under section 505(c) of the FFD&C Act (as distinguished from a drug approved in an ANDA under section 505(j) of the FFD&C Act) may be relied upon to support approval of a 505(b)(2) application, this 505(b)(2) application cannot rely upon Hi-Tech Syrup to support its approval.

Therefore, this 505(b)(2) application solely relies upon FDA's finding of safety and effectiveness for Hycodan Syrup (NDA 005213).

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22439	ORIG-1	CYPRESS PHARMACEUTICAL INC	(b) (4) (HYDROCODONE BITARTRATE/CHLORPH
NDA-22442	ORIG-1	CYPRESS PHARMACEUTICAL INC	REZIRA (b) (4) (HYDROCODONE BITARTRATE AND PSEU

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/s/

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KIM M Quaintance  
05/27/2010

## MEMORANDUM

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

**TO:** NDA 022439  
NDA 022442

**FROM:** Kim Quaintance  
Associate Director for Regulatory Affairs  
Office of New Drugs

**SUBJECT:** Addendum to 505(b)(2) Assessments

This memorandum seeks to further clarify the listed drug relied upon to support approval of the proposed 505(b)(2) applications.

The applicant for NDA 022439 and NDA 022442, Cypress Pharmaceuticals, Inc., (Cypress) cited reliance on FDA's finding of safety and effectiveness for Hycodan Syrup (NDA 005213, applicant: Endo Pharmaceuticals), Tussionex Extended Release Suspension (NDA 019111, applicant: UCB Inc), and Codeprex Extended Release Suspension (NDA 021369, applicant: UCB Inc) to support approval of its 505(b)(2) application in their original application received November 7, 2008 and November 10, 2008, respectively. In the applicant's responses to our Complete Response letters, Cypress added another listed drug relied upon to support approval of its 505(b)(2) applications: Hi-Tech Syrup (ANDA 040613, applicant: Hi Tech Pharmacal Co, Inc.) but did not indicate that it no longer sought to rely on Hycodan Syrup.

Hycodan Syrup is listed in the "Discontinued" section of the Orange Book, but was not withdrawn from sale for reasons of safety or effectiveness. Cypress conducted bioequivalence trials with Hycodan Syrup before it was discontinued.

As outlined in the (b)(2) assessments, while the applicant cited reliance on Tussionex and Codeprex, the review division determined that reliance on these two listed drugs was not necessary for approval of these (b)(2) applications.

Although it was approved in an ANDA, Hi-Tech Syrup is designated in the Orange Book as a reference listed drug (RLD) because Hycodan Syrup, the previous RLD, has been discontinued. Given that only a listed drug approved for safety and effectiveness under section 505(c) of the FFD&C Act (as distinguished from a drug approved in an ANDA under section 505(j) of the FFD&C Act) may be relied upon to support approval of a 505(b)(2) application, this 505(b)(2) application cannot rely upon Hi-Tech Syrup to support its approval.

Therefore, this 505(b)(2) application solely relies upon FDA's finding of safety and effectiveness for Hycodan Syrup (NDA 005213).

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22439	ORIG-1	CYPRESS PHARMACEUTICAL INC	(b) (4) (HYDROCODONE BITARTRATE/CHLORPH
NDA-22442	ORIG-1	CYPRESS PHARMACEUTICAL INC	REZIRA (b) (4) (HYDROCODONE BITARTRATE AND PSEU

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/s/

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KIM M Quaintance  
05/27/2010

**505(b)(2) ASSESSMENT**

<b>Application Information</b>		
NDA # 22-439	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: (b)(4) (proposed) Established/Proper Name: hydrocodone, chlorpheniramine, pseudoephedrine Dosage Form: oral solution Strengths: 5mg/4mg/60mg/ in 5 ml		
Applicant: Cypress Pharmaceutical, Inc.		
Date of Receipt: December 11, 2009		
PDUFA Goal Date: June 11, 2009		Action Goal Date (if different):
Proposed Indication(s): 1. Relief of cough and nasal congestion associated with common cold 2. Relief of symptoms including nasal congestion associated with upper respiratory allergies		

**GENERAL INFORMATION**

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?
- YES  NO

*If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*



**INFORMATION PROVIDED VIA RELIANCE  
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
NDA 05-213 <b>Hycodan</b>	Label Sections 1.0, 4.0, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 6.1, 7.1, 7.2, 8.1, 8.2, 8.3, 8.4, 8.6, 8.7, 8.8, 9.1, 9.2, 9.3, 10.1, 10.2, 12.1,
NDA 19-111 ** <b>Tussionex</b> Extended Release Suspension	Label Sections 5.4, 6.1, 8.5, 10.1, 12.1,
NDA 21-369 ** <b>Codeprex</b> Extended-Release Suspension	Label Sections 6.1, 7.3, 8.1, 8.3, 8.4, 10.1, 10.2, 13.1
<b>21 CFR 201.57(c)(3)</b> Specific requirements on content and format of labeling . . .	Label Section 8.1
<b>21 CFR 341.72</b> Labeling of antihistamine drug products	Label Sections 1.0, 2.1, 2.2, 5.5, 17.1
<b>21 CFR 341.80</b> Labeling of nasal decongestant drug products	Label Sections 1.0, 2.1, 2.2, 5.1, 5.6, 7.2, 17.1
Mosby Drug Reference **	Label Sections 12.1

\*each source of information should be listed on separate rows

\*\* Although the applicant cited reliance on this information in the cover letter and annotated labeling submitted in their original application, the review division has determined that reliance on this information is not necessary for approval.

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

**This application relies on a BA/BE study of the proposed product to the referenced products. No clinical studies for safety and efficacy were required to support this application.**

**RELIANCE ON PUBLISHED LITERATURE**

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES  NO   
*If "NO," proceed to question #5.*

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES  NO   
*If "NO", proceed to question #5.*  
*If "YES", list the listed drug(s) identified by name and answer question #4(c).*

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES  NO

### RELIANCE ON LISTED DRUG(S)

*Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.*

- 5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES  NO   
*If "NO," proceed to question #10.*

- 6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Hycodan	NDA 05-213	Y
Tussionex *	NDA 19-111	Y*
Tavist Allergy/Sinus *	NDA 21-082	Y*
Advil Allergy Sinus Caplets*	NDA 21-441	Y*

\*Although the applicant cited reliance on this information in the cover letter and annotated labeling submitted in their original application, the review division has determined that reliance on this information is not necessary for approval

*Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?  
N/A  YES  NO

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".*

*If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES  NO   
*If "YES", please list which drug(s)*

Name of drug(s) approved in a 505(b)(2) application: **Tavist Allergy/Sinus**

- b) Approved by the DESI process?

YES  NO   
*If "YES", please list which drug(s)*

Name of drug(s) approved via the DESI process: **Hycodan**

- c) Described in a monograph?

YES  NO   
*If "YES", please list which drug(s)*

Name of drug(s) described in a monograph:

**Chlorpheniramine, 21CFR §341.12**  
**Pseudoephedrine, 21 CFR §341.20**

- d) Discontinued from marketing?

YES  NO   
*If "YES", please list which drug(s) and answer question d) i. below.*  
*If "NO", proceed to question #9.*

Name of drug(s) discontinued from marketing: **Hycodan**

- i) Were the products discontinued for reasons related to safety or effectiveness?

YES  NO

*(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If*

*a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)*

- 9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsule to solution”).

**This application provides for a new combination drug product.**

*The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.*

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

- 10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; **and** (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).*

*Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES  NO

*If “NO” to (a) proceed to question #11.*

*If “YES” to (a), answer (b) and (c) then proceed to question #12.*

- (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES  NO

- (c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES  NO

*If “YES” to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*

*If “NO” or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all*

of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

*Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES  NO

If "NO", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES  NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES  NO

If "YES" and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

#### PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed  proceed to question #14

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES  NO

*If "NO", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

21 CFR 314.50(i)(1)(ii): No relevant patents.

21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES  NO

*If "NO", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES  NO

*If "NO", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

*Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES  NO  Patent owner(s) consent(s) to an immediate effective date of approval

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22439

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ORIG-1

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CYPRESS  
PHARMACEUTICA  
L INC

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(b) (4) (HYDROCODONE  
BITARTRATE/CHLORPH

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/s/  
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CAROL F HILL  
05/27/2010

**MEMORANDUM**

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

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DATE: May 20, 2010

TO: Badrul A. Chowdhury, M.D.  
Director  
Division of Pulmonary and Allergy Products (DPAP)  
Office of Drug Evaluation (HFD-570)

Chandrasah Sahajwalla, Ph.D.  
Director  
Division of Clinical Pharmacology-2  
Office of Clinical Pharmacology (HFD-870)

FROM: Carol M. Rivera-Lopez, Ph.D.  
Jacqueline A. O'Shaughnessy, Ph.D.  
Division of Scientific Investigations (HFD-48)

THROUGH: Martin K. Yau, Ph.D. \_\_\_\_\_  
Acting Team Leader, Bioequivalence  
GLP and Bioequivalence Branch  
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIR Covering NDA 22-439, (b)(4)  
(Hydrocodone, Chlorpheniramine, Pseudoephedrine) 5  
mg/4 mg/60 mg per 5 ml oral solution, sponsored by  
Cypress Pharmaceuticals, Inc.

At the request of the Division of Pulmonary and Allergy Products (DPAP), the Division of Scientific Investigations (DSI) conducted an audit of the clinical and analytical portions of the following studies:

**Study # S08-0179**

**Title:** "A relative bioavailability and drug-drug interaction study of hydrocodone, pseudoephedrine, and chlorpheniramine oral solution (5 mg/60 mg/4 mg per 5 ml), pseudoephedrine oral solution (60 mg per 5 ml), chlorpheniramine oral solution (4 mg per 5 ml) and HYCODAN<sup>®</sup> syrup (5 mg hydrocodone bitartrate/1.5 mg homatropine methylbromide per 5 ml) under fasted conditions"

**Study # SAM-09-1010**

**Title:** "A study to evaluate the relative bioavailability of hydrocodone bitartrate in a 5 mg/60 mg/4 mg hydrocodone bitartrate/pseudoephedrine HCl/chlorpheniramine maleate oral solution compared to Hi-Tech (1.5 mg/5 mg homatropine methylbromide/hydrocodone bitartrate) syrup in healthy subjects under fasted conditions"

The clinical portion of study SAM-09-1010 was conducted at (b)(4) and the analytical portion was conducted at (b)(4). The clinical portion of study S08-0179 was conducted at (b)(4) and the analytical portion was conducted at (b)(4).

**A review that included evaluation of the two clinical portions and the analytical portion of study SAM-09-1010 was submitted to DPAP on May 5, 2010. This memorandum covers only evaluation of the analytical portion of study S08-0179.**

In addition to the subject NDA, the inspection also included follow-up of the firm's investigation of a complaint received by the Agency in June of 2009, in which an ex-employee of (b)(4) alleged misconduct in a number of bioanalytical studies. The firm conducted and reported to the Agency the results of their internal review and a third party audit contracted to investigate the complaint allegations.

Following inspection of (b)(4) (May 3-7, 2010), Form FDA-483 was issued (Attachment 1). As of this memorandum, DSI has not received (b)(4) response to Form FDA-483. Our evaluation of the Form FDA-483 observations follows:

(b)(4)

**1. Records for the extraction of subject samples in numerous studies were falsified.**

As part of their internal investigation of the complaint allegations, (b)(4) found more than 1,900 instances where laboratory technicians identified as having conducted sample extractions were not present in the facility at the documented time of the study event. The firm identified this issue by comparing electronic records of card key building entry and

paper records of analytical batch processing. The falsification was pervasive for extractions conducted on weekends and holidays over the time period of April 2005 to June 2009 and affected numerous studies for multiple sponsors. Affected data for Study S08-0179 include Runs 11-16 for Hydrocodone/ Chlorpheniramine and Runs 11-18 for Pseudoephedrine (refer to Attachment 2 for details).

The DSI inspection found that (b)(4) review only considered extraction records with weekend/holiday dates<sup>1</sup>. In this regard, it is unknown if weekday extraction records were also falsified in a similar manner during the time period in question. Furthermore, although (b)(4) investigation and follow up suggests that the falsification is limited to the date/time of extraction (i.e., samples were actually extracted on Friday but documented as done over the weekend), the falsification itself questions the integrity of overall activities at this firm.

**Additional Complaint Issue:** The complainant also alleged that laboratory staff altered the outcome of analytical runs (i.e., runs were "fixed") through "prep" runs injected prior to the actual subject sample batch. (b)(4) suggested that the "prep" runs were actually intended to equilibrate the LC/MS systems. However, their investigation found unexplained discrepancies between the initial system equilibration result ("prep" run) and the actual run result in four runs from three studies. Specifically, "prep" run calibration standards had no drug or internal standard peak present yet the actual subject sample run had these peaks. (b)(4) stated that sponsors of the affected studies were notified that these runs should be excluded.<sup>2</sup> As the firm's investigation to date could not explain this discrepancy, falsification of analytical batches cannot be ruled out.

The DSI inspection also found that the firm's investigation was insufficient to thoroughly address the allegation of "fixing" runs. Specifically, the firm lacked adequate documentation and written procedures to verify the identity of samples in the "prep" runs. Instead, (b)(4) made assumptions

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<sup>1</sup> (b)(4) suggested that weekend/holiday activities had less supervisory oversight and there was an incentive program for weekend work.

<sup>2</sup> Four subject sample runs from three studies were affected; (b)(4) (b)(4)

about the identity of such samples for the conduct of their investigation<sup>3</sup> (Attachment 1 Form FDA-483 item 2). Given the lack of confirmatory information, it is not possible to determine if the firm's investigation could identify runs affected by "fixing" versus those without such manipulation.

The falsification of weekend extraction records and unexplained discrepancies with the "prep" runs are significant issues that raise concerns about the integrity of data generated by this site. As of this writing, (b)(4) response to the Form FDA-483 has not been received by DSI to determine what additional steps the firm will initiate to address the inspectional findings.

**2. Validation documentation was incomplete in that extraction times for some validation runs were not recorded and the storage location of stability samples to demonstrate freeze/thaw and long term stability was not documented.**

Due to insufficient source documentation for the freeze/thaw (F/T) and long term stability (LTS) evaluations, it was not possible to confirm that F/T and LTS were demonstrated under the necessary conditions. During the inspection, firm management agreed to this observation. DSI recommends that additional F/T and LTS data be generated with appropriate documentation.

In addition to the above observations, Attachment 3 includes two additional Form FDA-483 observations related to Study S08-0179; although these deficiencies require correction, study outcome should not be impacted significantly.

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<sup>3</sup> (b)(4) assumed that the "prep" run samples were the same as those subsequently injected in the actual subject sample batch because the electronic chromatography record used the same identifying details from the injection sequence. However, the identity of samples in the "prep" runs were not documented in the paper extraction record, such injections were not recorded in instrument log books, and the archived paper record did not include a printed copy of the "prep" run injections.

**Conclusions:**

Following the above inspection, the Division of Scientific Investigations recommends the following:

- Study S08-0179 should not be accepted for review at this time due to record falsification and incomplete investigation of complaint allegations by (b)(4) (item 1 above). Additional information from matters such as the firm's response, potential follow up inspection, and notification of Office of Criminal Investigations (OCI) are needed to determine the acceptability of data generated by the site for the five year time period of April 2005 to June 2009.
- Due to lack of source documentation, F/T and LTS determinations cannot be assured. Appropriate F/T and LTS data to demonstrate analyte stability under the same conditions as the subject samples (hydrocodone/chlorpheniramine/pseudoephedrine in combination) are needed.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

---

Carol M. Rivera-Lopez, Ph.D.

---

Jacqueline A. O'Shaughnessy, Ph.D.

**Final Classification:**

**OAI -** (b)(4) **FEI:** (b)(4)

cc:

CDER DSI PM TRACK (email)

DSI/Ball/Viswanathan

DSI/GLPBB/Rivera-Lopez/O'Shaughnessy/Yau/Haidar/CF

OND/ODE/DPAP/Bowen

OTS/OCP/DCP2/Xu/Shang

HFR-SW1580/Stone

Draft: CRL 5/11, 14, 18/10; JAO 5/17, 18/10

Edit: MKY 5/18/10; SHH 5/19/10

DSI file: 6039 O:\BIOEQUIV\EIRCOVER\22439rez.cyp.doc

FACTS: 1147409

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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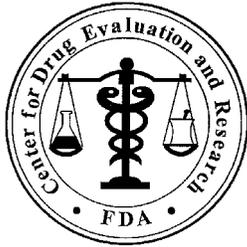
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CAROL M RIVERA-LOPEZ  
05/20/2010

JACQUELINE A O SHAUGHNESSY  
05/20/2010

MARTIN K YAU  
05/20/2010

SAM H HAIDAR  
05/24/2010



**Department of Health and Human Services**  
**Public Health Service**  
**Food and Drug Administration**  
**Center for Drug Evaluation and Research**  
**Office of Surveillance and Epidemiology**

Date: May 7, 2010

To: Badrul Chowdhury, MD, Director  
Division of Pulmonary, Allergy and Rheumatology Products

Through: Zachary Oleszczuk, PharmD, Acting Team Leader  
Denise Toyer, PharmD, Deputy Director  
Division of Medication Error Prevention and Analysis (DMEPA)

From: Felicia Duffy, RN, BSN, MSED, Safety Evaluator  
Division of Medication Error Prevention and Analysis (DMEPA)

Subject: Label and Labeling Review

Drug Name: (b) (4) (Hydrocodone Bitartrate, Chlorpheniramine Maleate,  
and Pseudoephedrine HCl) Oral Solution  
5 mg/4 mg/60 mg per 5 mL

Application Type/Number: NDA 022439

Applicant: Cypress Pharmaceuticals

OSE RCM #: 2009-2441

## 1 INTRODUCTION

This review is written in response to a request from the Division of Pulmonary, Allergy, and Rheumatology Products for the assessment of labels and labeling for (b) (4) (Hydrocodone bitartrate, Chlorpheniramine maleate, and Pseudoephedrine HCl) Oral Solution for their vulnerability to medication errors.

## 2 METHODS AND MATERIALS

The Division of Medication Error Prevention and Analysis (DMEPA) used Failure Mode and Effects Analysis<sup>1</sup> (FMEA) in our evaluation of the container label, carton labeling and insert labeling that were submitted by the Applicant on November 6, 2008 and resubmitted on December 10, 2009 (see Appendices A and B; no image of insert labeling).

## 3 RECOMMENDATIONS

Our evaluation noted areas where information on the label and labeling can be clarified and improved upon to minimize the potential for medication errors. Section 3.1 (*Comments to the Division*) contains our recommendations for the insert labeling. Section 3.2 (*Comments to the Applicant*) contains our recommendations for the container label and carton labeling. We request these recommendations be communicated to the Applicant prior to approval.

We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Carolyn Volpe, OSE Regulatory Project manager, at 301-796-5204.

### 3.1 COMMENTS TO THE DIVISION

We note that the dose is presented in (b) (4) milliliters throughout the insert labeling (e.g., 5 mL (b) (4)). Since the insert is geared towards healthcare providers, we recommend presenting the dose only in the metric units (i.e., mL) in order to avoid dosing errors or confusion (b) (4).

### 3.2 COMMENTS TO THE APPLICANT

#### A. Container Label ((b) (4) and 480 mL)

1. As currently presented, the (b) (4) between Rezira and (b) (4) container labels may increase the potential for shelf selection errors if the products are stored by established name. Therefore, in order to minimize the potential for selection errors, use a (b) (4) for Rezira and (b) (4).

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<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.

2. The thin font used for the established name and product strength is difficult to read because the letters appear compacted. Revise the font of the established name and product strength in order to improve readability.
3. As currently presented, the product strength (5 mg/4 mg/60 mg per 5 mL) is not prominent and is difficult to find. Increase the prominence of the product strength by highlighting, boxing, color, or some other means. Additionally, add white space between the established name and product strength in order to increase the prominence of the product strength.
4. The principle display panel of the 480 mL container label appears cluttered. Relocate the contents statement to the side panel to provide more room to increase the prominence of the product strength.
5. The contents statement is confusing (b) (4) (see below).

(b) (4)

Since practitioners can calculate the amount (b) (4) and in order to avoid confusion, we recommend deleting the (b) (4) since the concentration of the product is per 5 mL. Revise the (b) (4) column to delete (b) (4) and revise the statement of strength as follows:

**Contains:**

Hydrocodone  
 Bitartrate.....5 mg/5 mL

**Warning: May be habit forming.**

Chlorpheniramine  
 Maleate.....4 mg/5 mL

Pseudoephedrine  
 Hydrochloride.....60 mg/5 mL

6. Delete following statement on the side panel of the 480 mL container label: (b) (4)

**B. Carton Labeling ( (b) (4) sample, 12 count)**

1. See Comments A3 and A5.
2. The thin white font on the purple background containing the established name, product strength, usual dosage information, and warning information is difficult to read. Revise the prominence of the font in order to increase its readability.

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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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/s/

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FELICIA DUFFY  
05/07/2010

ZACHARY A OLESZCZUK  
05/07/2010

DENISE P TOYER  
05/07/2010

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications**

**\*\*\*Pre-decisional Agency Information\*\*\***

## Memorandum

**Date:** May 10, 2010

**To:** Carol Hill, Regulatory Project Manager  
Division of Pulmonary, Allergy, and Rheumatology Products  
(DPARP)

**From:** Roberta Szydlo, Regulatory Review Officer  
Division of Drug Marketing, Advertising, and Communications  
(DDMAC)

**Through:** Lisa Hubbard, Professional Group Leader

**CC:** Sangeeta Vaswani, DTC Group Leader  
Robyn Tyler, Regulatory Review Officer  
Wayne Amchin, Regulatory Health Project Manager  
(DDMAC)

**Subject:** NDA # 022439  
DDMAC labeling comments for Hydrocodone bitartrate,  
Chlorpheniramine maleate, and Pseudoephedrine  
hydrochloride Oral Solution

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DDMAC has reviewed the revised proposed product labeling (PI) for NDA 022439 submitted for consult on December 23, 2009. DDMAC's comments are based on the proposed draft marked-up labeling titled "N22439\_TRADENAME Oral Solution\_FDA Labeling edits May 5.doc" that was sent via email from DPARP to DDMAC on May 5, 2010.

DDMAC's comments on the PI are provided directly in the marked-up document attached (see below).

Thank you for the opportunity to comment on these proposed materials.

If you have any questions regarding the PI, please contact Roberta Szydlo at (301) 796-5389 or [roberta.szydlo@fda.hhs.gov](mailto:roberta.szydlo@fda.hhs.gov).

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CYPRESS  
PHARMACEUTICA  
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(b) (4) (HYDROCODONE  
BITARTRATE/CHLORPH

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/s/  
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ROBERTA T SZYDLO  
05/10/2010

MEMORANDUM

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

DATE: May 05, 2010

TO: Badrul A. Chowdhury, M.D.  
Director, Division of Pulmonary and Allergy Products  
Office of Drug Evaluation (HFD-570)

Chandrasah Sahajwalla, Ph.D.  
Director, Division of Clinical Pharmacology-2  
Office of Clinical Pharmacology (HFD-870)

FROM: Arindam Dasgupta, Ph.D.  
Division of Scientific Investigations (HFD-48)

THROUGH: Martin K. Yau, Ph.D. *Martin K. Yau 5/5/10*  
Acting Team Leader - Bioequivalence  
GLP & Bioequivalence Branch  
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIR Covering NDA 22-439, (b)(4)  
(hydrocodone, chlorpheniramine, pseudoephedrine) Oral  
Solution Sponsored by Cypress Pharmaceutical, Inc.

At the request of the Division of Pulmonary and Allergy Products (DPAP), the Division of Scientific Investigations (DSI) audited both the clinical and analytical portions of the following bioequivalence (BE) studies:

**STUDY-1:S08-0179**

**Study Title** "A relative bioavailability and drug-drug interaction study of hydrocodone, pseudoephedrine and chlorpheniramine oral solution (5 mg /60 mg/4 mg per 5 mL), pseudoephedrine oral solution(60 mg per 5 mL), chlorpheniramine oral solution(4 mg per 5 mL) and Hycodan~ syrup (5 mg hydrocodone bitartrate / 1.5 mg homatropine methylbromide per 5 ml) under fasted conditions"

**STUDY-2:SAM-09-1010**

**Study Title** "A study to evaluate the relative bioavailability of hydrocodone bitartrate in a 5 mg / 60 mg / 4 mg hydrocodone bitartrate / pseudoephedrine HCl /chlorpheniramine maleate oral

Page 2 - NDA 22-439, (b)(4) (hydrocodone, chlorpheniramine, pseudoephedrine) Oral Solution

solution compared to hi-tech (1.5 mg / 5 mg homatropine methyl bromide / hydrocodone bitartrate) syrup in healthy subjects under fasted conditions"

**Clinical and Analytical Site Audit (STUDY-1:S08-0179)**

The inspection of the clinical portions of the study S08-0179 was conducted at (b)(4) from March 16-17, 2010. Following the clinical site inspection at (b)(4) there were no significant findings and no Form FDA-483 was issued. **Please note that the audit of the analytical portion of the study is underway at (b)(4) and expected to finish by the first week of May, 2010.** Our evaluation of the inspectional findings of the analytical site inspection will be provided after audit of the analytical portion is complete.

**Clinical and Analytical Site Audit (STUDY-2: SAM-09-1010)**

The inspection of the clinical portion of the study SAM-09-1010 was conducted at (b)(4) (April 21-29, 2010). Form FDA-483 was issued at the clinical site (Attachment 1). At the time of this writing, the establishment inspection report (EIR) has not been received at DSI for the clinical site inspection. This evaluation is based upon the form FDA-483 observations and communications with the ORA investigator. DSI will provide DPAP an addendum if additional issues are identified in the EIR. The audit of the analytical portion of this study was conducted at (b)(4) (April 5-9, 2010). Form FDA-483 was issued (Attachment 2). The firm's response was received on April 29, 2010 (Attachment 3).

**Clinical Site:** (b)(4)  
**(STUDY-2)**

**1. An investigation was not conducted in accordance with the signed statement of investigator. Specifically, protocol SAM-9-1010 was not always followed for various protocol requirements. Additionally, there is no record that the IRB was notified and approved the deviations/violations (please see Attachment 1 for specific examples).**

The review division should evaluate the impact of use of concomitant medications (Mirtazapine, Premarin and Zoloft) by some subjects during the study. The other observations are not likely to impact study outcome.

**2. Failure to report promptly to the IRB all unanticipated problems involving risk to human subjects or others. Specifically, there is no record of notification to the IRB regarding any problems or adverse events (please see Attachment 1 for specific examples).**

The firm recorded the adverse events, but they were not reported to the IRB. Although these findings should not impact study outcome, nevertheless, the firm should take corrective action to prevent the above issues from repeating in future studies.

**3. Investigational drug disposition records are not adequate with respect to quantity and use by subjects. Specifically, drug dispensing records do not always indicate whether the investigational drug was used or returned to the Pharmacy. (please see Attachment 1 for specific examples).**

Although the above Form FDA-483 observations cited documentation issues, these findings did not have any impact on study outcome.

**Analytical Site: (b)(4)(STUDY-2)**

**1. Failure to adequately document all aspects of study conduct. (Please see attachment 2 for specific examples)**

The firm did not maintain source records or documentation for most of the activities related to pre-study method validation. Proper documentation is critical to reconstructing the study conduct. The firm claimed that the analyst performed the pre-study method validation activities as per their SOP. This practice is objectionable as in absence of source documentation, pre-study method validation activities could not be confirmed.

In their response (b)(4) acknowledged the form FDA-483 observation and promised corrective action. The firm has modified their SOPs to require proper documentation of all study related activities in their source records.

**2. Stability samples used for processed sample stability validation were not compared against freshly extracted calibrators.**

In their response, the firm agreed to modify their SOP to require fresh calibrators for determination of extract stability. The firm however did not provide any additional data

to demonstrate processed sample stability against a freshly extracted standard curve.

**3. For validation batch HCM1130a, chromatograms with the original integration before the manual change were not maintained, and justification for the manual reintegration was not documented.**

Specifically, chromatograms for five selectivity samples for hydrocodone were manually modified.

(b)(4) acknowledged the findings. The firm promised to modify their SOP so that for future studies, justification for manual reintegration was documented.

**4. Failure to establish objective criteria to consistently calculate mean internal standard (IS) response. For example, for analytical batch HydroG66, mean IS response was calculated based on the IS response of the calibration standards, whereas in batch HydroG85A, mean IS response was calculated from the IS response of the QCs. The justification for how mean IS response was calculated was also not documented.**

Although the finding is not likely to affect the acceptability of the reported concentrations, the firm should follow a consistent practice.

The firm has acknowledged the observation and has modified their SOP to prevent inconsistency in calculation of mean IS response and to require proper documentation of the justification if the mean IS response is calculated otherwise.

**Conclusions:**

Due to the absence of source documentation at (b)(4) (see discussion in analytical 483, Item 1 and attachment 2), the experiments conducted as part of pre-study method validations cannot be assured. Hence the bioequivalence data for study SAM-09-1010 submitted in the NDA are questionable.

To assure accuracy of bioequivalence data in study SAM-09-1010, the sponsor should provide new stability data (including frozen Long-term, freeze-thaw, refrigerated, room-temperature and processed stability) to support integrity of the BE data generated in the study. The data needs to be generated while

Page 5 - NDA 22-439, (b)(4) (hydrocodone, chlorpheniramine, pseudoephedrine) Oral Solution

maintaining complete source documentation for all the stability experiments.

DSI recommends that the clinical data from Studies S08-0179 and SAM-09-1010 be accepted for review.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

*Arindam Dasgupta 5/5/10*

Arindam Dasgupta, Ph.D.

**Final Classifications:**

NAI- (b)(4)

VAI- (b)(4)

VAI- (b)(4)

cc: DARRTS  
OND/ODE/DPAP/ Chowdhury/ Philantha M. Bowen  
OTS/OCP/DCP2/ Sahajwalla  
OCP/DCP2/Xu/Shang  
OC/DSI/Haidar/Dasgupta/Yau/O' Shaughnessy/Rivera-Lopez

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SW-FO/KAN-DO/ thuy.nguyen2@fda.hhs.gov

Draft: AD 05/05/10  
Edits: MKY 05/05/10  
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FACTS: 1147409

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/s/  
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ARINDAM DASGUPTA

05/05/2010

# DSI CONSULT

## Request for Biopharmaceutical Inspections

**DATE:** January 26, 2010

**TO:** Associate Director for Bioequivalence  
Division of Scientific Investigations, HFD-48

**FROM:** Philantha M. Bowen, Regulatory Project Manager, Division of Pulmonary and Allergy Products, HFD-570

**SUBJECT: Request for Biopharmaceutical Inspections**  
NDA 22439  
(b)(4) (hydrocodone, chlorpheniramine, pseudoephedrine) Oral Solution

**Study/Site Identification:**

As discussed with you, the following studies/sites pivotal to approval (OR, raise question regarding the quality or integrity of the data submitted and) have been identified for inspection:

Study #	Clinical Site (name, address, phone, fax, contact person, if available)	Analytical Site (name, address, phone, fax, contact person, if available)
S08-0179	(b)(4)	
SAM-09-1010	(b)(4)	

**International Inspections:**

**(Please note: International inspections require sign-off by the ORM Division Director or DPE Division Director.)**

We have requested an international inspection because:

There is a lack of domestic data that solely supports approval;

Other (please explain):

**Goal Date for Completion:**

We request that the inspections be conducted and the Inspection Summary Results be provided by April 4, 2010. We intend to issue an action letter on this application by **June 11, 2010**.

Should you require any additional information, please contact Philantha M. Bowen, Regulatory Project Manager, at 301-796-2466.

Concurrence: (Optional)

Yun Xu, M.D., Ph.D., Clinical Pharmacology Team Leader (Acting)

Elizabeth Shang, Ph.D., Clinical Pharmacology Reviewer

Application  
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Submission  
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PHILANTHA M BOWEN  
01/26/2010

505(b)(2) ASSESSMENT

Application Information		
NDA # 22-439	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: (b) (4)	Established/Proper Name: hydrocodone, chlorpheniramine, pseudoephedrine	
Dosage Form: oral solution		
Strengths: 5mg/4mg/60mg/ in 5 ml		
Applicant: Cypress Pharmaceutical, Inc.		
Date of Receipt: November 7, 2008		
PDUFA Goal Date: September 7, 2009		Action Goal Date (if different): September 17, 2009
Proposed Indication(s):	(b) (4) (b) (4)	

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product OR is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES  NO

*If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*



**INFORMATION PROVIDED VIA RELIANCE  
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
NDA 05-213 <b>Hycodan</b>	Label Sections 1.0, 4.0, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 6.1, 7.1, 7.2, 8.1, 8.2, 8.3, 8.4, 8.6, 8.7, 8.8, 9.1, 9.2, 9.3, 10.1, 10.2, 12.1,
NDA 19-111 ** <b>Tussionex</b> Extended Release Suspension	Label Sections 5.4, 6.1, 8.5, 10.1, 12.1,
NDA 21-369 ** <b>Codeprex</b> Extended-Release Suspension	Label Sections 6.1, 7.3, 8.1, 8.3, 8.4, 10.1, 10.2, 13.1
<b>21 CFR 201.57(c)(3)</b> Specific requirements on content and format of labeling . . .	Label Section 8.1
<b>21 CFR 341.72</b> Labeling of antihistamine drug products	Label Sections 1.0, 2.1, 2.2, 5.5, 17.1
<b>21 CFR 341.80</b> Labeling of nasal decongestant drug products	Label Sections 1.0, 2.1, 2.2, 5.1, 5.6, 7.2, 17.1
Mosby Drug Reference **	Label Sections 12.1

\*each source of information should be listed on separate rows

\*\* Although the applicant cited reliance on this information in the cover letter and annotated labeling submitted in their original application, the review division has determined that reliance on this information is not necessary for approval.

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

**This application relies on a BA/BE study of the proposed product to the referenced products. No clinical studies for safety and efficacy were required to support this application.**

**RELIANCE ON PUBLISHED LITERATURE**

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES  NO   
 If "NO," proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES  NO   
 If "NO", proceed to question #5.  
 If "YES", list the listed drug(s) identified by name and answer question #4(c).

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES  NO

**RELIANCE ON LISTED DRUG(S)**

*Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.*

- 5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES  NO   
 If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Hycodan	NDA 05-213	Y
Tussionex *	NDA 19-111	Y*
Tavist Allergy/Sinus *	NDA 21-082	Y*
Advil Allergy Sinus Caplets*	NDA 21-441	Y*

\*Although the applicant cited reliance on this information in the cover letter and annotated labeling submitted in their original application, the review division has determined that reliance on this information is not necessary for approval

*Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?  
N/A  YES  NO

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".*

*If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES  NO   
*If "YES", please list which drug(s)*

Name of drug(s) approved in a 505(b)(2) application: **Tavist Allergy/Sinus**

- b) Approved by the DESI process?

YES  NO   
*If "YES", please list which drug(s)*

Name of drug(s) approved via the DESI process: **Hycodan**

- c) Described in a monograph?

YES  NO   
*If "YES", please list which drug(s)*

Name of drug(s) described in a monograph:

**Chlorpheniramine, 21CFR §341.12**  
**Pseudoephedrine, 21 CFR §341.20**

- d) Discontinued from marketing?

YES  NO   
*If "YES", please list which drug(s) and answer question d) i. below.*  
*If "NO", proceed to question #9.*

Name of drug(s) discontinued from marketing: **Hycodan**

- i) Were the products discontinued for reasons related to safety or effectiveness?

YES  NO

*(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If*

*a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)*

- 9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

**This application provide for a new combination drug product.**

*The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.*

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

- 10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; **and** (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).*

*Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES  NO

*If "NO" to (a) proceed to question #11.*

*If "YES" to (a), answer (b) and (c) then proceed to question #12.*

- (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES  NO

- (c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES  NO

*If "YES" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*

*If "NO" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all*

of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

*Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES  NO

If "NO", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES  NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES  NO

If "YES" and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

#### PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed  proceed to question #14

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES  NO

*If "NO", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

21 CFR 314.50(i)(1)(ii): No relevant patents.

21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES  NO

*If "NO", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES  NO

*If "NO", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

*Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES  NO  Patent owner(s) consent(s) to an immediate effective date of approval

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22439

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ORIG-1

-----  
CYPRESS  
PHARMACEUTICA  
L INC

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(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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PHILANTHA M BOWEN  
09/17/2009

MEMORANDUM

Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research

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**Date:** September 11, 2009

**To:** Badrul Chowdhury, M.D., Ph.D. Director  
Division of Pulmonary and Allergy Products

**Through:** Michael Klein, Ph.D., Director  
Controlled Substance Staff (CSS)

**From:** Lori A. Love, M.D. Ph.D., Lead Medical Officer, CSS

**Subject:** CSS Recommendations:  
\* NDA 22-439 - (b)(4) (hydrocodone, chlorpheniramine, &  
pseudoephedrine) Oral Solution  
\* NDA 22-442 - REZIRA (b)(4) (hydrocodone & pseudoephedrine) Oral  
Solution,

**Materials reviewed:** Materials submitted and comprising the NDAs that CSS was consulted on. Minutes of the Regulatory Briefing on Abuse Potential Safety Testing for Hydrocodone Cough and Cold Combination Products held June 12, 2009. The OSE Review of August 26, 2009.

The Controlled Substance Staff (CSS) was consulted on NDAs for hydrocodone combination products currently under review in the Division of Pulmonary and Allergy Products (DPAP). CSS was asked to assess these products for abuse potential and for scheduling status under the Controlled Substances Act (CSA). Dr. James Tolliver (Pharmacologist, CSS) responded by memo of September 3, 2009 (NDA 22-439 and NDA 22-442). In a subsequent discussion between CSS and DPAP, CSS determined that further clarification of the recommendations was appropriate.

The recommendations below are also relevant to the following submissions: (b)(4)  
[REDACTED]  
[REDACTED] NDA 22-476 -  
HISTUSSIN HC (phenylephrine, hydrocodone, & chlorpheniramine) Syrup.

**Recommendation**

CSS recommends that each Sponsor conduct active surveillance and monitoring of their respective drug products for signals of abuse, misuse, overdose and addiction. The Sponsor should provide periodic analysis and summary of surveillance and monitoring

activities for abuse, misuse, overdose, and addiction for a period of five years. The Sponsor should provide periodic assessments for the first 6 months post approval and then annually unless a signal is identified. Outcomes and any interventions that were taken should be described.

### **Discussion**

Drug abuse data bases show that hydrocodone is one of the most abused opioid drugs in the United States. In addition, medical examiner reports show that hydrocodone is associated with many deaths. Over the past several years on numerous occasions, FDA/CDER has been requested to respond to regulatory issues dealing with the abuse, misuse, addiction, and overdose of hydrocodone. In order to differentiate the abuse potential of distinct hydrocodone products, CSS proposed that animal and human abuse liability laboratory pharmacology studies be conducted pre-approval. The regulatory briefing panel did not see the need for any laboratory abuse studies for the individual products, unless the individual product had demonstrated a signal for abuse. At present, there is a problem with generation of such a signal for any of the individual products. The Office of Surveillance and Epidemiology (OSE) consult discussed the signal limitations in its review. Applying the evidence found in the Drug Abuse Warning Network (DAWN), OSE advised that the abuse of the hydrocodone cough-cold products appears to be lower than for analgesic hydrocodone products. However, because of the data limitations, OSE recommended that further abuse liability assessment be conducted post-approval on all hydrocodone containing cough cold products submitted as NDAs.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22442	ORIG-1	CYPRESS PHARMACEUTICA L INC	REZIRA <sup>(b)</sup> <sub>(4)</sub> (HYDROCODONE BITARTRATE AND PSEU

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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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LORI A LOVE  
09/11/2009

MICHAEL KLEIN  
09/11/2009



**MEMORANDUM**  
**Department of Health and Human Services**  
**Food and Drug Administration**  
**Center for Drug Evaluation and Research**

**Date:** September 3, 2009

**To:** Badrul Chowdhury, M.D., Ph.D. Director  
Division of Pulmonary and Allergy Products

**Through:** Michael Klein, Ph.D., Director  
Controlled Substance Staff (CSS)

Lori A. Love, M.D. Ph.D., Lead Medical Officer, CSS

**From:** James M. Tolliver, Ph.D., Pharmacologist, CSS  
Controlled Substance Staff (CSS)

**Subject:** Consult on NDAs 22-439 for [REDACTED] (b)(4) (hydrocodone, chlorpheniramine, and pseudoephedrine) Oral Solution and 22-442 for REZIRA [REDACTED] (b)(4) (hydrocodone and pseudoephedrine) Oral Solution Sponsor: Cypress Pharmaceuticals, Inc..

**Materials reviewed:** All materials submitted and comprising NDA 22-439 and NDA 22-442. Minutes of the Regulatory Briefing on Abuse Potential Safety Testing for Hydrocodone Cough and Cold Combination Products held June 12, 2009 and the OSE Review of August 26, 2009.

**Background:**

Cypress Pharmaceuticals, Inc. (Sponsor) submitted for approval to the FDA NDA 22-439 for [REDACTED] (b)(4) Oral Solution and NDA 22-442 for REZIRA [REDACTED] (b)(4) Oral Solution. The Sponsor is using the 505(b)(2) regulatory pathway with reliance on DESI Notice #5213 (37 F.R. 7827), reference products Hycodan (NDA 5-213) and Tussionex Extended-Release Suspension (NDA 19-111), medical literature and the OTC Monographs for chlorpheniramine maleate and pseudoephedrine HCl. On January 14, 2008, the Sponsor met with the FDA to discuss requirements for [REDACTED] (b)(4) [REDACTED] Oral Solution and REZIRA [REDACTED] (b)(4) Oral Solution. Based upon an examination of the minutes of this meeting dated February 6, 2008, there was no discussion of the abuse potential or scheduling for these products. At the request of the Division of Pulmonary & Allergy Products, CSS reviewed both NDAs for abuse potential and recommendation for drug scheduling.

[REDACTED] (b)(4) Oral Solution is formulated such that [REDACTED] (b)(4) (5 mL) contains: hydrocodone bitartrate, 5 mg; chlorpheniramine maleate, 4 mg; and pseudoephedrine

hydrochloride, 60 mg. The product is indicated for (b) (4)  
(b) (4)  
(b) (4). For adults (b) (4)  
(b) (4), the dosage regimen is (b) (4) (5 mL) every 4 to 6 hours as  
needed, not to exceed 4 doses (20 mL) in 24 hours. (b) (4)

(b) (4) (5 mL) of REZIRA (b) (4) Oral Solution contains hydrocodone bitartrate,  
5 mg; and pseudoephedrine hydrochloride, 60 mg. The product is indicated for the (b) (4)  
(b) (4). For adults (b) (4), the dosage regimen is (b) (4)  
(5 mL) every 4 to 6 hours as needed, not to exceed 4 doses (20 mL) in 24 hours. (b) (4)

Currently, all marketed hydrocodone products are formulated as hydrocodone in combination with a nonnarcotic drug present in a recognized therapeutic amount, and are in Schedule III of the Controlled Substances Act. These drug combinations are intended either for the treatment of pain or for cough suppression and cold symptom relief. Two products, namely Tussionex Pennkinetic and Tussicaps, that contain hydrocodone in combination with chlorpheniramine maleate are used for the relief of cough and upper respiratory symptoms associated with allergy or a cold in adults and children 6 years of age or older. There are no currently approved products that contain hydrocodone in combination with pseudoephedrine HCl.

### CSS Conclusions

In light of the review conducted and described under “CSS Review”, CSS makes the conclusions listed below.

- (b) (4) Oral Solution and REZIRA (b) (4) Oral Solution meet the statutory definition for Schedule III control in the Controlled Substances Act.
- The available information in the public domain indicates that hydrocodone alone and in combination with other substances each have an abuse potential.
- The Sponsor has not provided in the NDA specific data pertaining to the abuse potential of (b) (4) Oral Solution and REZIRA (b) (4) Oral Solution which are needed for evaluation of safety and labeling.

### CSS Recommendations

- The Sponsor needs to fully characterize the abuse potential of both (b) (4) Oral Solution and REZIRA (b) (4) Oral Solution, specifically to evaluate how the

addition of the nonnarcotic components (chlorpheniramine and pseudoephedrine) affects the abuse potential of the products relative to hydrocodone alone which is listed as a Schedule II substance in the CSA.

- Therefore the Sponsor should assess the abuse potential and actual abuse of the drug products. Such assessments are necessary to fully determine the appropriate scheduling and safety profile of these products.
- CSS will review protocols and provide comments to the Sponsor prior to beginning studies.

## CSS Review

### Abuse Potential of (b) (4) Oral Solution and REZIRA (b) (4) Oral Solution

CSS is not aware of any products that are currently marketed and are formulated similar to that of (b) (4) Oral Solution and REZIRA (b) (4) Oral Solution. According to “Clinical Pharmacology Online” the products “Detussin”, H Tuss D”, “Hytussin” and “Iotussin” did not have approved NDAs and not marketed. These products were formulated as oral solutions containing 5 mg hydrocodone and 60 mg pseudoephedrine HCl per 5 mL of solution. No products were identified specifically formulated as oral solutions containing 5 mg hydrocodone, 4 mg chlorpheniramine and 60 mg pseudoephedrine HCl per 5 mL of oral solution.

The Sponsor utilized post-marketing data and labeling information for Hycodan and Tussionex to indicate that (b) (4) Oral Solution and REZIRA (b) (4) Oral Solution have an abuse potential. No preclinical or clinical studies of abuse potential were conducted on the products and provided in the NDAs submitted by the Sponsor.

With the exception of an FDA Public Health Advisory entitled “Important Information for the Safe Use of Tussionex Pennkinetic Extended-Release Suspension” suggesting some misuse of Tussionex, CSS has not found specific abuse related information regarding hydrocodone in combination with chlorpheniramine and/or pseudoephedrine. In order to evaluate the possible abuse potential of (b) (4) Oral Solution and REZIRA (b) (4) Oral Solution, CSS has examined information relevant to hydrocodone, (including hydrocodone combination products), and to chlorpheniramine and pseudoephedrine.

The information reviewed by CSS predicts that (b) (4) Oral Solution and REZIRA (b) (4) Oral Solution does have an abuse potential and as such will be associated with abuse, misuse, overdoses and the development of physical dependence with possible severe withdrawal syndrome. In addition, the combination of hydrocodone and chlorpheniramine may lead in particular to adverse effects associated with central nervous system depression. With regard to potential abuse and misuse of these products there is an increased concern regarding safety and proper labeling.

### *Hydrocodone*

Both preclinical and clinical studies show that hydrocodone has abuse potential. Hydrocodone as the individual substance has a high potential for abuse and is in Schedule II of the Controlled Substances Act.

Preclinical studies provide evidence of a potential for abuse of hydrocodone. Eddy and Reid (1934) showed that repeated administration of hydrocodone produced dependence in dogs and monkeys. In two studies using rats, hydrocodone shows complete stimulus generalization to fentanyl (Meert and Vermeersch, 2005) and to morphine (Tomkins et al., 1997). Hydrocodone also maintains intravenous self-administration behavior in rats (Tomkins et al., 1997), thereby demonstrating reinforcing efficacy.

Clinical and epidemiological reports and controlled clinical abuse liability studies attest to the potential for abuse of hydrocodone either alone or in combination with other substances. Early clinical studies document the abuse and addiction of hydrocodone in individuals given hydrocodone either for pain or as an antitussive (for review, see Eddy et al., 1957). Nonmedical use, including abuse, of hydrocodone containing products is also documented in a number of epidemiological reports including reports utilizing data from the Drug Abuse Warning Network (DAWN) and the National Survey on Drug Use and Health (NSDUH) (Hughes et al., 2007; Becker et al., 2008; Butler et al., 2008; Havens et al., 2008; Kelly et al., 2008; Wu et al., 2008).

One noncontrolled study (Fraser and Isbell, 1950) and three controlled abuse liability clinical studies (Zacny, 2003; Zacny et al., 2005; Walsh et al., 2008) using subjects with a history of drug abuse demonstrate that hydrocodone either alone or in combination with acetaminophen or with homatropine (Hycodan) produces subjective reinforcing effects similar to those of other opioids and that are predictive of abuse liability.

CSS has also examined data concerning hydrocodone derived from DAWN and NSDUH. According to DAWN, in 2007 there were an estimated 65,734 emergency department episodes involving the nonmedical use, including abuse, of hydrocodone combination products. According to NSDUH, in 2007, an estimated 21,335,000 individuals reported the nonmedical use of hydrocodone products at least once in their lifetime.

### *Chlorpheniramine*

Chlorpheniramine is a first generation histamine antagonist associated with an abuse potential. It displays stimulus generalization to cocaine (Suzuki et al., 1997; Zacny, 1989) but not to morphine (Suzuki et al., 1997). It also maintains intravenous self-administration behavior in Rhesus monkeys at a level consistent with limited reinforcing efficacy (Beardsley and Balster, 1992). Further evidence of reinforcing efficacy is the ability of chlorpheniramine to evoke conditioned place preference in laboratory animals (Suzuki et al., 1999; Zimmermann et al., 1999; Hasenohrl et al., 2001) which is antagonized by dopamine 1 receptor antagonists (Suzuki et al., 1999). Suzuki et al. (1990) show that chlorpheniramine significantly potentiates the conditioned place

preference evoked by the opioid, dihydrocodeine, thereby suggesting a potentiation of the reinforcing efficacy of the opioid. Chlorpheniramine is also reported to produce effects on dopamine neurotransmission consistent with that of drugs of abuse (Tanda et al., 2008).

Information on abuse and misuse of chlorpheniramine maleate is limited. Recently, Mahanta et al. (2008), reported that in the Mumbai/Thane district of India, heroin (99%) and avil (chlorpheniramine maleate) (87%) were the two main drugs injected by intravenous drug abusers. In Japan, abuse of an over-the-counter antitussive product containing dihydrocodeine, chlorpheniramine, methylephedrine and caffeine is reported (Murao et al., 2008, Tani et al., 1984). The extent to which chlorpheniramine contributes to the abuse of this product is not clear. However, in preclinical studies chlorpheniramine is shown to potentiate the reinforcing properties of dihydrocodeine in a conditioned place preference study (Suzuki et al., 1990) and to suppress development of physical dependence to dihydrocodeine (Suzuki et al., 1988). Finally, in recent years abuse of Coricidin HBP tablets containing chlorpheniramine in combination with dextromethorphan is reported to be abused, particularly among adolescents (Bryner et al., 2006; Dickerson et al., 2008). The extent to which chlorpheniramine contributes to the abuse of the product is not known and has not been studied.

Support for the idea that a first generation antihistamine combined with an opioid can provoke abuse is evident in the case of pentazocine combined with the first generation antihistamine, tripeleminamine. Particularly in the 1970s, this combination, sold illegally as “T’s and Blues” was widely abused by heroin addicts (Lahmeyer and Steingold, 1980; Poklis and Whyatt, 1980; Debard and Jagger, 1981). More recently, heroin combined with the first generation antihistamine, diphenhydramine, as well as acetaminophen, was distributed in the illicit drug market under the street name of “Cheese” in the United States, particularly in the Southwest (Erowid website).

### *Pseudoephedrine*

Pseudoephedrine is considered to have a relatively low potential for abuse. At high doses pseudoephedrine generalizes to amphetamine (Tongjaroenbuangam et al., 1998). Isomers of pseudoephedrine display weak reinforcing efficacy as evidenced by their ability at high doses to maintain intravenous self-administration behavior in Rhesus monkeys and to interact with the dopamine transporter (Wee et al., 2004). There is little information on actual abuse of pseudoephedrine.

### Scheduling of (b) (4) Oral Solution and REZIRA (b) (4) Oral Solution

While hydrocodone substance is in Schedule II of the Controlled Substances Act, hydrocodone combination products currently approved for use in the United States are placed in Schedule III, pursuant to 21 U.S.C. 812(c)(Schedule III)(d)(4). This provision of the CSA specifies that unless specifically excepted or unless listed in another schedule, any material, compound, mixture, or preparation is in Schedule III, if it contains not more

than 300 milligrams of hydrocodone per 100 milliliters or not more than 15 milligrams per dosage unit, with one or more active, nonnarcotic ingredients in recognized therapeutic amounts. Both (b)(4) Oral Solution and REZIRA (b)(4) Oral Solution meet the requirements of this provision for Schedule III control

For both (b)(4) Oral Solution and REZIRA (b)(4) Oral Solution, the concentration of hydrocodone is less than 300 mg per 100 mL. Chlorpheniramine and pseudoephedrine are nonnarcotics substances as they do not fit the definition for a “narcotic drug” found in 21 U.S.C. 802(17).

Finally, (b)(4) Oral Solution and REZIRA (b)(4) Oral Solution each meet the criterion that the nonnarcotic ingredients are present in recognized therapeutic amounts. Information from the product formulation and dosage regimen, as well as from the OTC Drug Monograph for pseudoephedrine HCl (21 CFR 341.20(a)(2) and 21 CFR 341.80(d)(1)(ii)) and for chlorpheniramine maleate (21 CFR 341.12(c) and 21 CFR 341.72(d)(3)) indicate that the pseudoephedrine HCl and chlorpheniramine maleate present in (b)(4) Oral Solution are at therapeutic doses as a nasal decongestant and antihistamine, respectively. Information from the product formulation and dosage regimen, as well as from the OTC Drug Monograph (21 CFR 341.20 and 21 CFR 341.80(d)(1)(ii)), indicate that pseudoephedrine HCl present in REZIRA (b)(4) Oral Solution is at a therapeutic dose as a nasal decongestant.

## References

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JAMES M TOLLIVER  
09/03/2009

MICHAEL KLEIN  
09/03/2009



**MEMORANDUM**  
**Department of Health and Human Services**  
**Food and Drug Administration**  
**Center for Drug Evaluation and Research**

**Date:** September 3, 2009

**To:** Badrul Chowdhury, M.D., Ph.D. Director  
Division of Pulmonary and Allergy Products

**Through:** Michael Klein, Ph.D., Director  
Controlled Substance Staff (CSS)

Lori A. Love, M.D. Ph.D., Lead Medical Officer, CSS

**From:** James M. Tolliver, Ph.D., Pharmacologist, CSS  
Controlled Substance Staff (CSS)

**Subject:** Consult on NDAs 22-439 for [REDACTED] (b)(4) (hydrocodone, chlorpheniramine, and pseudoephedrine) Oral Solution and 22-442 for REZIRA (b)(4) (hydrocodone and pseudoephedrine) Oral Solution Sponsor: Cypress Pharmaceuticals, Inc..

**Materials reviewed:** All materials submitted and comprising NDA 22-439 and NDA 22-442. Minutes of the Regulatory Briefing on Abuse Potential Safety Testing for Hydrocodone Cough and Cold Combination Products held June 12, 2009 and the OSE Review of August 26, 2009.

**Background:**

Cypress Pharmaceuticals, Inc. (Sponsor) submitted for approval to the FDA NDA 22-439 for [REDACTED] (b)(4) Oral Solution and NDA 22-442 for REZIRA (b)(4) Oral Solution. The Sponsor is using the 505(b)(2) regulatory pathway with reliance on DESI Notice #5213 (37 F.R. 7827), reference products Hycodan (NDA 5-213) and Tussionex Extended-Release Suspension (NDA 19-111), medical literature and the OTC Monographs for chlorpheniramine maleate and pseudoephedrine HCl. On January 14, 2008, the Sponsor met with the FDA to discuss requirements for [REDACTED] (b)(4) Oral Solution and REZIRA (b)(4) Oral Solution. Based upon an examination of the minutes of this meeting dated February 6, 2008, there was no discussion of the abuse potential or scheduling for these products. At the request of the Division of Pulmonary & Allergy Products, CSS reviewed both NDAs for abuse potential and recommendation for drug scheduling.

[REDACTED] (b)(4) Oral Solution is formulated such that [REDACTED] (b)(4) (5 mL) contains: hydrocodone bitartrate, 5 mg; chlorpheniramine maleate, 4 mg; and pseudoephedrine

hydrochloride, 60 mg. The product is indicated for (b) (4)  
(b) (4)  
(b) (4). For adults (b) (4)  
(b) (4), the dosage regimen is (b) (4) (5 mL) every 4 to 6 hours as  
needed, not to exceed 4 doses (20 mL) in 24 hours. (b) (4)

(b) (4) (5 mL) of REZIRA (b) (4) Oral Solution contains hydrocodone bitartrate,  
5 mg; and pseudoephedrine hydrochloride, 60 mg. The product is indicated for the (b) (4)  
For adults (b) (4), the dosage regimen is (b) (4) 1  
(5 mL) every 4 to 6 hours as needed, not to exceed 4 doses (20 mL) in 24 hours. (b) (4)

Currently, all marketed hydrocodone products are formulated as hydrocodone in combination with a nonnarcotic drug present in a recognized therapeutic amount, and are in Schedule III of the Controlled Substances Act. These drug combinations are intended either for the treatment of pain or for cough suppression and cold symptom relief. Two products, namely Tussionex Pennkinetic and Tussicaps, that contain hydrocodone in combination with chlorpheniramine maleate are used for the relief of cough and upper respiratory symptoms associated with allergy or a cold in adults and children 6 years of age or older. There are no currently approved products that contain hydrocodone in combination with pseudoephedrine HCl.

### CSS Conclusions

In light of the review conducted and described under “CSS Review”, CSS makes the conclusions listed below.

- (b) (4) Oral Solution and REZIRA (b) (4) Oral Solution meet the statutory definition for Schedule III control in the Controlled Substances Act.
- The available information in the public domain indicates that hydrocodone alone and in combination with other substances each have an abuse potential.
- The Sponsor has not provided in the NDA specific data pertaining to the abuse potential of (b) (4) Oral Solution and REZIRA (b) (4) Oral Solution which are needed for evaluation of safety and labeling.

### CSS Recommendations

- The Sponsor needs to fully characterize the abuse potential of both (b) (4) Oral Solution and REZIRA (b) (4) Oral Solution, specifically to evaluate how the

addition of the nonnarcotic components (chlorpheniramine and pseudoephedrine) affects the abuse potential of the products relative to hydrocodone alone which is listed as a Schedule II substance in the CSA.

- Therefore the Sponsor should assess the abuse potential and actual abuse of the drug products. Such assessments are necessary to fully determine the appropriate scheduling and safety profile of these products.
- CSS will review protocols and provide comments to the Sponsor prior to beginning studies.

### CSS Review

#### Abuse Potential of (b) (4) Oral Solution and REZIRA (b) (4) Oral Solution

CSS is not aware of any products that are currently marketed and are formulated similar to that of (b) (4) Oral Solution and REZIRA (b) (4) Oral Solution. According to “Clinical Pharmacology Online” the products “Detussin”, H Tuss D”, “Hytussin” and “Iotussin” did not have approved NDAs and not marketed. These products were formulated as oral solutions containing 5 mg hydrocodone and 60 mg pseudoephedrine HCl per 5 mL of solution. No products were identified specifically formulated as oral solutions containing 5 mg hydrocodone, 4 mg chlorpheniramine and 60 mg pseudoephedrine HCl per 5 mL of oral solution.

The Sponsor utilized post-marketing data and labeling information for Hycodan and Tussionex to indicate that (b) (4) Oral Solution and REZIRA (b) (4) Oral Solution have an abuse potential. No preclinical or clinical studies of abuse potential were conducted on the products and provided in the NDAs submitted by the Sponsor.

With the exception of an FDA Public Health Advisory entitled “Important Information for the Safe Use of Tussionex Pennkinetic Extended-Release Suspension” suggesting some misuse of Tussionex, CSS has not found specific abuse related information regarding hydrocodone in combination with chlorpheniramine and/or pseudoephedrine. In order to evaluate the possible abuse potential of (b) (4) Oral Solution and REZIRA (b) (4) Oral Solution, CSS has examined information relevant to hydrocodone, (including hydrocodone combination products), and to chlorpheniramine and pseudoephedrine.

The information reviewed by CSS predicts that (b) (4) Oral Solution and REZIRA (b) (4) Oral Solution does have an abuse potential and as such will be associated with abuse, misuse, overdoses and the development of physical dependence with possible severe withdrawal syndrome. In addition, the combination of hydrocodone and chlorpheniramine may lead in particular to adverse effects associated with central nervous system depression. With regard to potential abuse and misuse of these products there is an increased concern regarding safety and proper labeling.

### *Hydrocodone*

Both preclinical and clinical studies show that hydrocodone has abuse potential. Hydrocodone as the individual substance has a high potential for abuse and is in Schedule II of the Controlled Substances Act.

Preclinical studies provide evidence of a potential for abuse of hydrocodone. Eddy and Reid (1934) showed that repeated administration of hydrocodone produced dependence in dogs and monkeys. In two studies using rats, hydrocodone shows complete stimulus generalization to fentanyl (Meert and Vermeersch, 2005) and to morphine (Tomkins et al., 1997). Hydrocodone also maintains intravenous self-administration behavior in rats (Tomkins et al., 1997), thereby demonstrating reinforcing efficacy.

Clinical and epidemiological reports and controlled clinical abuse liability studies attest to the potential for abuse of hydrocodone either alone or in combination with other substances. Early clinical studies document the abuse and addiction of hydrocodone in individuals given hydrocodone either for pain or as an antitussive (for review, see Eddy et al., 1957). Nonmedical use, including abuse, of hydrocodone containing products is also documented in a number of epidemiological reports including reports utilizing data from the Drug Abuse Warning Network (DAWN) and the National Survey on Drug Use and Health (NSDUH) (Hughes et al., 2007; Becker et al., 2008; Butler et al., 2008; Havens et al., 2008; Kelly et al., 2008; Wu et al., 2008).

One noncontrolled study (Fraser and Isbell, 1950) and three controlled abuse liability clinical studies (Zacny, 2003; Zacny et al., 2005; Walsh et al., 2008) using subjects with a history of drug abuse demonstrate that hydrocodone either alone or in combination with acetaminophen or with homatropine (Hycodan) produces subjective reinforcing effects similar to those of other opioids and that are predictive of abuse liability.

CSS has also examined data concerning hydrocodone derived from DAWN and NSDUH. According to DAWN, in 2007 there were an estimated 65,734 emergency department episodes involving the nonmedical use, including abuse, of hydrocodone combination products. According to NSDUH, in 2007, an estimated 21,335,000 individuals reported the nonmedical use of hydrocodone products at least once in their lifetime.

### *Chlorpheniramine*

Chlorpheniramine is a first generation histamine antagonist associated with an abuse potential. It displays stimulus generalization to cocaine (Suzuki et al., 1997; Zacny, 1989) but not to morphine (Suzuki et al., 1997). It also maintains intravenous self-administration behavior in Rhesus monkeys at a level consistent with limited reinforcing efficacy (Beardsley and Balster, 1992). Further evidence of reinforcing efficacy is the ability of chlorpheniramine to evoke conditioned place preference in laboratory animals (Suzuki et al., 1999; Zimmermann et al., 1999; Hasenohrl et al., 2001) which is antagonized by dopamine 1 receptor antagonists (Suzuki et al., 1999). Suzuki et al. (1990) show that chlorpheniramine significantly potentiates the conditioned place

preference evoked by the opioid, dihydrocodeine, thereby suggesting a potentiation of the reinforcing efficacy of the opioid. Chlorpheniramine is also reported to produce effects on dopamine neurotransmission consistent with that of drugs of abuse (Tanda et al., 2008).

Information on abuse and misuse of chlorpheniramine maleate is limited. Recently, Mahanta et al. (2008), reported that in the Mumbai/Thane district of India, heroin (99%) and avil (chlorpheniramine maleate) (87%) were the two main drugs injected by intravenous drug abusers. In Japan, abuse of an over-the-counter antitussive product containing dihydrocodeine, chlorpheniramine, methylephedrine and caffeine is reported (Murao et al., 2008, Tani et al., 1984). The extent to which chlorpheniramine contributes to the abuse of this product is not clear. However, in preclinical studies chlorpheniramine is shown to potentiate the reinforcing properties of dihydrocodeine in a conditioned place preference study (Suzuki et al., 1990) and to suppress development of physical dependence to dihydrocodeine (Suzuki et al., 1988). Finally, in recent years abuse of Coricidin HBP tablets containing chlorpheniramine in combination with dextromethorphan is reported to be abused, particularly among adolescents (Bryner et al., 2006; Dickerson et al., 2008). The extent to which chlorpheniramine contributes to the abuse of the product is not known and has not been studied.

Support for the idea that a first generation antihistamine combined with an opioid can provoke abuse is evident in the case of pentazocine combined with the first generation antihistamine, tripelemnamine. Particularly in the 1970s, this combination, sold illegally as “T’s and Blues” was widely abused by heroin addicts (Lahmeyer and Steingold, 1980; Poklis and Whyatt, 1980; Debard and Jagger, 1981). More recently, heroin combined with the first generation antihistamine, diphenhydramine, as well as acetaminophen, was distributed in the illicit drug market under the street name of “Cheese” in the United States, particularly in the Southwest (Erowid website).

### *Pseudoephedrine*

Pseudoephedrine is considered to have a relatively low potential for abuse. At high doses pseudoephedrine generalizes to amphetamine (Tongjaroenbuangam et al., 1998). Isomers of pseudoephedrine display weak reinforcing efficacy as evidenced by their ability at high doses to maintain intravenous self-administration behavior in Rhesus monkeys and to interact with the dopamine transporter (Wee et al., 2004). There is little information on actual abuse of pseudoephedrine.

### Scheduling of (b) (4) Oral Solution and REZIRA (b) (4) Oral Solution

While hydrocodone substance is in Schedule II of the Controlled Substances Act, hydrocodone combination products currently approved for use in the United States are placed in Schedule III, pursuant to 21 U.S.C. 812(c)(Schedule III)(d)(4). This provision of the CSA specifies that unless specifically excepted or unless listed in another schedule, any material, compound, mixture, or preparation is in Schedule III, if it contains not more

than 300 milligrams of hydrocodone per 100 milliliters or not more than 15 milligrams per dosage unit, with one or more active, nonnarcotic ingredients in recognized therapeutic amounts. Both (b)(4) Oral Solution and REZIRA (b)(4) Oral Solution meet the requirements of this provision for Schedule III control

For both (b)(4) Oral Solution and REZIRA (b)(4) Oral Solution, the concentration of hydrocodone is less than 300 mg per 100 mL. Chlorpheniramine and pseudoephedrine are nonnarcotics substances as they do not fit the definition for a “narcotic drug” found in 21 U.S.C. 802(17).

Finally, (b)(4) Oral Solution and REZIRA (b)(4) Oral Solution each meet the criterion that the nonnarcotic ingredients are present in recognized therapeutic amounts. Information from the product formulation and dosage regimen, as well as from the OTC Drug Monograph for pseudoephedrine HCl (21 CFR 341.20(a)(2) and 21 CFR 341.80(d)(1)(ii)) and for chlorpheniramine maleate (21 CFR 341.12(c) and 21 CFR 341.72(d)(3)) indicate that the pseudoephedrine HCl and chlorpheniramine maleate present in (b)(4) Oral Solution are at therapeutic doses as a nasal decongestant and antihistamine, respectively. Information from the product formulation and dosage regimen, as well as from the OTC Drug Monograph (21 CFR 341.20 and 21 CFR 341.80(d)(1)(ii)), indicate that pseudoephedrine HCl present in REZIRA (b)(4) Oral Solution is at a therapeutic dose as a nasal decongestant.

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JAMES M TOLLIVER  
09/03/2009

LORI A LOVE  
09/03/2009

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09/03/2009



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: July 30, 2009

To: Corinne P. Moody  
Science Policy Analyst  
Controlled Substances Staff

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Subject: Epidemiological Analysis of Hydrocodone containing Products

Drug Name(s): hydrocodone containing products

Submission Number: various

Application Number: (b)(4) 22-439

OSE RCM #: 2009-1034

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## **EXECUTIVE SUMMARY**

The Controlled Substances Staff (CSS) is evaluating the abuse of respiratory (cough and cold) hydrocodone products that, to date, have been marketed without approval. In support of that evaluation, the Office of Surveillance and Epidemiology (OSE), Division of Epidemiology (DEPI) has been requested to evaluate data from the Drug Abuse Warning Network (DAWN) as well as prescription utilization data for all hydrocodone containing products.

This analysis uses dispensed prescriptions for hydrocodone containing products using SDI, Vector One®: National (VONA) and DAWN, a public health surveillance system that examines drug related emergency room visits to conduct its analysis.

National estimates were provided for emergency department (ED) visits associated with hydrocodone containing products stratified into: analgesic products, and respiratory products. Two types of ED visits associated with hydrocodone containing products were provided: adverse reaction, and all misuse/abuse (AllMA) were examined. An adverse reaction ratio and an “abuse ratio” were calculated by dividing the number of ED visits for each event by 10,000 prescriptions. Lastly, the number of non-medical use ED visits per adverse reaction ED visits (i.e. therapeutic use) was calculated to examine reasons why patients arrive in the ED, i.e. is it for non-medical or for therapeutic reasons.

The number of AllMA ED visits (n=245,297) as well adverse reaction ED visits (n=182,182) associated with analgesic hydrocodone products is large when compared to the total number of ED visits associated with respiratory hydrocodone products, (n=10,374). After adjusting for drug utilization however, these differences attenuate somewhat for adverse reaction ED visits (4.1/10,000 prescriptions for analgesic products vs. (1.9/10,000 prescriptions for respiratory products) and remain large for AllMA visits (5.5/10,000 prescriptions for analgesic products vs. 0.5/10,000 prescriptions for respiratory products.)

Using the limited evidence found in DAWN, the abuse of respiratory hydrocodone products appears to be lower than for analgesic hydrocodone products. Given significantly lower rates of drug utilization and evidence that some albeit much lower, abuse ratios were found with these products, OSE/DEPI makes the following recommendations for additional studies:

- 1) Abuse liability studies should be required of the sponsors submitting NDA’s
- 2) Conducting these studies post-approval is appropriate
- 3) Without more information on the different molecular entities, the studies should be conducted on all respiratory hydrocodone containing products

## **1 BACKGROUND**

### **1.1 INTRODUCTION**

The Controlled Substances Staff (CSS) is evaluating the abuse of respiratory hydrocodone products that, to date, have been marketed without approval. In support of that evaluation, the Office of Surveillance and Epidemiology (OSE), Division of

Epidemiology (DEPI) has been requested to provide data from the Drug Abuse Warning Network (DAWN) as well as prescription utilization data for all hydrocodone containing products grouped as respiratory (cough/cold) and analgesic products for years 2004 through 2007.

The rationale for this request was in response to the Regulatory Briefing: Abuse Liability Testing for Hydrocodone Combination Products held on June 12, 2009. CSS was consulted on NDAs for hydrocodone cough cold combination products currently under review in the Division of Pulmonary and Allergy Products (DPAP). CSS believes that abuse potential studies should be performed on the hydrocodone products to support labeling and appropriate scheduling.

This recommendation, however, raised questions regarding whether to require abuse potential studies on hydrocodone combination products, and the regulatory briefing was conducted to answer the following questions:

- 1) Should abuse potential assessment be required for hydrocodone containing combination products for cough/cold/allergy indications?
- 2) If so, should the abuse potential assessment be required for approval or performed post-approval?
- 3) Should abuse potential assessment be required for all hydrocodone containing combination products for cough/cold/allergy indication or on a case by case basis?

At the regulatory briefing, it was determined that the sponsors of these products should be required to conduct abuse liability studies. These studies could be conducted post-approval and that the requirement for abuse potential assessment would be required on a case by case basis.

This analysis focuses on current epidemiological data of non-medical use of hydrocodone containing products using data obtained from the Drug Abuse Warning Network (DAWN) and drug utilization data obtained from SDI, Vector One®.

## **2 METHODS AND MATERIALS**

### **2.1 DATA AND INFORMATION SOURCES**

#### **2.1.1 SDI, Vector One®: National (VONA)**

Proprietary drug use databases licensed by the Agency were used to conduct this analysis.

We examined total dispensed prescriptions for hydrocodone containing products using SDI, Vector One®: National (VONA) (see Appendix 1 for full description) for calendar years 2004 through 2007.

#### **2.2 DRUG ABUSE WARNING NETWORK (DAWN)**

DAWN, administered by the Substance Abuse and Mental Health Services Administration (SAMHSA), is an active public health surveillance system that examines drug related emergency room visits. DAWN monitors drug-related visits to hospital emergency departments (ED) and provides data on patients treated in hospital emergency departments. Drug-related ED visits are found by retrospective review of medical

records in a national sample of hospitals. Hospitals eligible for DAWN include non-Federal, short-term, general hospitals that operate 24-hour EDs.

## **2.3 CRITERIA USED**

### **2.3.1 Outpatient Dispensed Prescriptions -- VONA**

Table A.1 in the Appendix shows the total number of prescriptions dispensed in the outpatient retail setting (mail order excluded) for hydrocodone containing products. During year 2007, approximately (b) (4) prescriptions were dispensed for products containing hydrocodone of which approximately (b) (4) were dispensed for hydrocodone analgesic combinations and (b) (4) for hydrocodone cough and cold products. For both hydrocodone analgesic and hydrocodone cough and cold products, the number of prescriptions dispensed (b) (4) from year 2004 to 2007.

### **2.3.2 Drug Abuse Warning Network (DAWN)**

CSS requested and obtained national estimates of drug related ED visits for hydrocodone containing for the years 2004 – 2007. Estimates were provided for ED visits associated with hydrocodone containing products broken out into three different categories: analgesic, respiratory products as well as estimates for both analgesic and respiratory (cough and cold) products combined. The drug combinations that were included in each of these categories can be found in Table A.3 of the Appendix.

One of the data elements recorded in DAWN includes “type of case”. Specific types for DAWN ED visits include suicide attempts, overmedication, adverse reactions, accidental ingestions, malicious poisoning, and patients seeking detoxification or drug abuse treatment and drug abuse and misuse, entered as “other”.

Three types of ED visits associated with hydrocodone containing products were provided: adverse reaction, all misuse/abuse (AllMA) and nonmedical use of pharmaceuticals (NMUP). AllMA and NMUP are constructs that combine various types of cases recorded in DAWN. NMUP: includes: ED visits where the patient exceeded prescribed or recommended dose i.e. overmedication, used drugs prescribed for another person, malicious poisoning (always very low numbers) or substance abuse which is categorized by “other”. AllMA is a more comprehensive category than NMUP; it includes all NMUP visits plus any visits where hydrocodone was present with an illicit drug or with alcohol.

Adverse reaction visits are drug-related ED visits that are the consequences of using a prescription or over-the-counter drug for therapeutic purposes. It includes ED visits related to adverse drug reactions, side effects, drug-drug interactions, and drug-alcohol interactions. Adverse reactions that involve a pharmaceutical with an illicit drug are exceptions and are excluded from this category.

It is important to note that, in DAWN, national estimates are not provided for all the data requested. If the relative standard error (RSE)<sup>1</sup> is greater than 50, national estimates cannot be provided because the confidence intervals are too large and there is too much imprecision in the estimate. Estimates were requested by ten-year age bands and for case disposition, in many cases, these data were suppressed due to RSE's greater than 50. As a result, ages of patients as well as case disposition were not analyzed because there were too many suppressed estimates. Likewise, there were numerous missing values for visits considered to be NMUP visits so AllMA visits (as well as adverse reaction) were used for this analysis.

## **2.4 ANALYSIS TECHNIQUES/STEPS**

This analysis utilizes data obtained from the DAWN as well as data on drug utilization obtained from SDI Vector One®.

Two types of ED visits were examined in this analysis to determine reasons why patients who use hydrocodone-containing products go to the ED: therapeutic- (adverse reaction) or non-medical- (misuse/abuse) related visits or both. Since the number of emergency room visits may be the result of greater drug utilization, i.e. greater drug exposure, drug utilization data were incorporated into this analysis. An “abuse ratio” was calculated by dividing the number of ED visits by 10,000 prescriptions. A similar ratio was computed for adverse reactions by dividing the number adverse reaction ED visits by 10,000 prescriptions.

Lastly, the number of non-medical use ED visits per adverse reaction ED visits (i.e. therapeutic use) was calculated to examine the reason why patients arrive in the ED primarily i.e. is it non-medical use or is for therapeutic reasons. There were large differences in the number of adverse reactions reported in 2004 compared to other years; these differences are likely the result of more training for the medical extractors collecting these data after the first year (2004) on the major changes implemented to the DAWN database.

## **3 RESULTS**

Table 3.1 shows the national estimates of “AllMA” (i.e. all misuse/abuse) ED visits associated with analgesic and respiratory hydrocodone containing products as well as “abuse ratios” for each category. There were 46,924 ED visits in 2004. The number increased (65%) to 77,560 visits in 2007 for analgesic hydrocodone products. The number of AllMA ED visits associated with respiratory hydrocodone products ranged from 389 ED visits in 2004 to 616 ED visits in 2007. It is important to note, that the RSE for the estimates for respiratory combination products in 2004 – 2006 were too large to produce confidence intervals and the estimates themselves cannot be regarded as precise ones.

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<sup>1</sup> Relative standard error is calculated by dividing the standard error of the estimate by the estimate itself, then multiplying that result by 100. Relative standard error is expressed as a percent of the estimate.

The numbers of prescriptions sold for analgesic hydrocodone products increased from (b) (4) prescriptions in 2004 to (b) (4) prescriptions in 2007 (b) (4). The number of prescriptions for respiratory hydrocodone products were considerably lower (b) (4)

The “abuse” ratios, for analgesic hydrocodone products increased from 4.3 ED visits per 10,000 prescriptions in 2004 to 5.8 ED visits per 10,000 prescriptions in 2007 (35%). For respiratory hydrocodone products, the ratios were somewhat variable and considerably lower, it ranged from a low of 0.3 ED visits per 10,000 prescriptions in 2005 to the highest ratio being 0.9 ED visits per 10,000 prescriptions in 2006. The results show an increasing trend for AllMA ED visits over time despite adjusting for use with respiratory products containing hydrocodone,

**Table 3.1: National Estimates of all abuse/misuse (AllMA) ED Visits Reported in DAWN and Number of ED Visits per 10,000 Prescriptions for Analgesic and Respiratory Hydrocodone Containing Products -- 2004 -2007**

AllMA ED Visits	2004	2005	2006	2007
Analgesic and Respiratory Products	46,924	56,037	67,043	77,560
95% CI	(35,536, 58,312)	(40,319, 71,756)	(52,019, 82067)	(59,306, 95,814)
Analgesic combinations	46,535	55,704	66,114	76,945
95% CI	(35,191, 57,878)	(39,939, 71,467)	(51,212, 81,015)	(58,712, 95,178)
Respiratory combinations	389	333	929	616
95% CI	...	...	...	(116, 1,115)
<b>Hydrocodone Prescriptions</b>				
Analgesic and Respiratory Products t	109,738,552	120,091,780	126,492,450	133,228,908
Analgesic Products	100,322,326	108,207,757	115,680,718	122,929,534
Respiratory Products	9,416,226	11,884,023	10,811,732	10,299,374
<b>Abuse Ratios*</b>				
Analgesic and Respiratory Products	4.3	4.7	5.3	5.8
Analgesic Products	4.6	5.1	5.7	6.3
Respiratory Products	0.4	0.3	0.9	0.6

\*abuse ratio = number of ED visits/10,000 prescriptions

... confidence intervals are not provided, if RSE is greater than 50

\*\* confidence intervals could not be obtained, estimates are considered to be imprecise

Source: SDI: Vector One © National, Extracted 7/09 and Office of Applied Studies, SAMHSA, Drug Abuse Warning Network

Table 3.2 shows the national estimates of Adverse Reaction ED visits associated with analgesic and respiratory hydrocodone containing products as well as “abuse ratios” for each category. There were 26,756 ED visits in 2004. The number increased to 64,779 visits (142%) in 2007 for analgesic hydrocodone products. The number of Adverse Reaction ED visits associated with respiratory hydrocodone products ranged from 2,086 ED visits in 2004 and 1,831 ED visits in 2007 and varied inconsistently by year. It is important to note, that the RSE for the estimates in 2004 – 2006 for the hydrocodone

respiratory products were too large to produce confidence intervals and the estimates themselves cannot be regarded as precise ones.

The adverse reaction ratios, for analgesic hydrocodone products were 2.4 ED visits per 10,000 prescriptions in 2004 and increased to 4.9 ED visits per 10,000 prescriptions in 2007 (104%). For respiratory hydrocodone products, the ratios ranged irregularly over the four years from a low of 1.7 in 2005 to a high of 2.2 in 2004 visits per 10,000 prescriptions.

**Table 3.2: National Estimates of Adverse Reaction ED Visits Reported in DAWN and Number of Adverse Reaction ED Visits per 10,000 Prescriptions for Analgesic and Respiratory Hydrocodone Containing Products -- 2004 - 2007**

<i>Total Adverse Reaction ED Visits</i>	<i>2004<sup>+</sup></i>	<i>2005</i>	<i>2006</i>	<i>2007</i>
Analgesic and Respiratory Products	26,756	44,221	54,533	64,779
Confidence Intervals	(17,141, 36,370 )	(32,363, 56079 )	(41,806, 67,260)	(47,688, 81,869)
Analgesic combinations	24,670	42,258	52,307	62,948
Confidence Intervals	(16,387, 32,952)	(31,040, 53,475)	(40,457, 64,156)	(46,527, 79,368)
Respiratory combination**	2,086	1,963	2,226	1,831
Confidence Intervals	...	...	...	...
<b>Hydrocodone Prescriptions</b>				
TOTAL Hydrocodone Market	<b>109,738,552</b>	<b>120,091,780</b>	<b>126,492,450</b>	<b>133,228,908</b>
Analgesic Products	100,322,326	108,207,757	115,680,718	122,929,534
Respiratory Products	9,416,226	11,884,023	10,811,732	10,299,374
<b>Adverse Reaction Ratios*</b>				
Both Analgesic and Respiratory Products	<b>2.4</b>	<b>3.7</b>	<b>4.3</b>	<b>4.9</b>
Analgesic Products	2.5	3.9	4.5	5.1
Respiratory Products	2.2	1.7	2.1	1.8

\*adverse reaction ratio = number of ED visits/10,000 prescriptions

... confidence intervals are not provided, if RSE is greater than 50

\*\* confidence intervals could not be obtained, estimates are considered to be imprecise

+ difference in the number of adverse reactions reported from 2004 to other years are the result of training of medical extractors

Source: SDI: Vector One ® National, Extracted 7/09 and Office of Applied Studies, SAMHSA, Drug Abuse Warning Network

Table 3.3 is a summary the number of non-medical AllMA ED visits per Adverse Reaction ED visits for analgesic and respiratory hydrocodone containing products for the years 2004 -2007. Except for 2004, the ratio of AllMA (abuse/misuse) visits per Adverse Reaction visits remained relatively constant over time.

Finally, there were approximately 1.3 NMUP visits per adverse reaction case for analgesic hydrocodone products and 0.3 NMUP visits per adverse reaction case for respiratory hydrocodone products.

**Table 3.3: National Estimates of All Medical Abuse (AllMA) and Adverse Reaction ED Visits Reported in DAWN and All Non-Medical Use ED Visits per Adverse Reaction ED Visits for Analgesic and Respiratory Hydrocodone Containing Products -- 2004 -2007**

<i>AllMA ED Visits</i>	<b>2004</b>	<b>2005</b>	<b>2006</b>	<b>2007</b>
Analgesic and Respiratory Products	<b>46,924</b>	<b>56,037</b>	<b>67,043</b>	<b>77,560</b>
Analgesic Hydrocodone/combinations	46,535	55,704	66,114	76,945
ED visits -- Respiratory Hydrocodone /combinations	389	333	929	616
<i>Adverse Reactions ED Visits</i> <sup>+</sup>				
Analgesic and Respiratory Products	<b>26,756</b>	<b>44,221</b>	<b>54,533</b>	<b>64,779</b>
Analgesic Hydrocodone/combinations	24,670	42,258	52,307	62,948
ED visits -- Respiratory Hydrocodone /combination**	2,086	1,963	2,226	1,831
<i>AllMA ED Visits per Adverse Reaction ED Visits</i>				
Analgesic and Respiratory Products	<b>1.8</b>	<b>1.3</b>	<b>1.2</b>	<b>1.2</b>
Analgesic Hydrocodone/combinations	1.9	1.3	1.3	1.2
ED visits -- Respiratory Hydrocodone /combination**	0.2	0.2	0.4	0.3

\*adverse reaction ratio = number of ED visits/10,000 prescriptions

<sup>+</sup> difference in the number of adverse reactions reported from 2004 to other years are the result of training of ED reporters

Source: SDI: Vector One ® National, Extracted 7/09 and Office of Applied Studies, SAMHSA, Drug Abuse Warning Network

#### 4 DISCUSSION

As can be seen in Table 1, the number of AllMA ED visits and adverse reaction ED visits associated with analgesic hydrocodone products is large compared to the number of ED visits associated with respiratory hydrocodone products and increases over time. However, after adjusting for drug utilization these differences attenuate for adverse reaction ED visits and, although lower, the increase over time remains for AllMA visits.

It is important to note the following limitations of this analysis. The estimates provided are not true ratios or rates. Each dataset (DAWN and SDI VONA) has different sampling methodologies, different populations and different methods for calculating point estimates and respective confidence intervals. Furthermore, these data are not linked, that for each dataset, data is collected independently. The individuals who went to the emergency room may not have had a prescriptions for the drugs associated with the ED visit. Therefore, the observations are ecological associations only.

Another important limitation is that DAWN data represent patients that were able to make it to the emergency room. Any differential in the risk of death that occurs prior to the ED visits will not be captured using DAWN ED data. Conversely, it is also possible that abuse of these cough and cold products does not result in an ED visit. Lastly, this analysis provides one estimate that includes a variety of respiratory hydrocodone combinations and as a result, inferences between these products cannot be made.

#### 5 CONCLUSIONS

There is limited evidence of drug abuse for respiratory hydrocodone products. The use of these products, however, is somewhat low and some misuse/abuse is still found in DAWN. Therefore, OSE/DEPI recommends to examine this issue further.

## **6 RECOMMENDATIONS**

Based on the limited evidence found in DAWN, the abuse of respiratory hydrocodone products appears to be lower than for analgesic hydrocodone products. Given significantly lower rates of drug utilization and evidence that some albeit much lower, abuse ratios were found with these products, OSE/DEPI makes the following recommendations for additional studies:

- 4) Abuse liability studies should be required of the sponsors submitting NDA's
- 5) Conducting these studies post-approval is appropriate
- 6) Without more information on the different molecular entities, the studies should be conducted on all respiratory hydrocodone containing products

**APPENDIX**

***SDI Vector One®: National (VONA)***

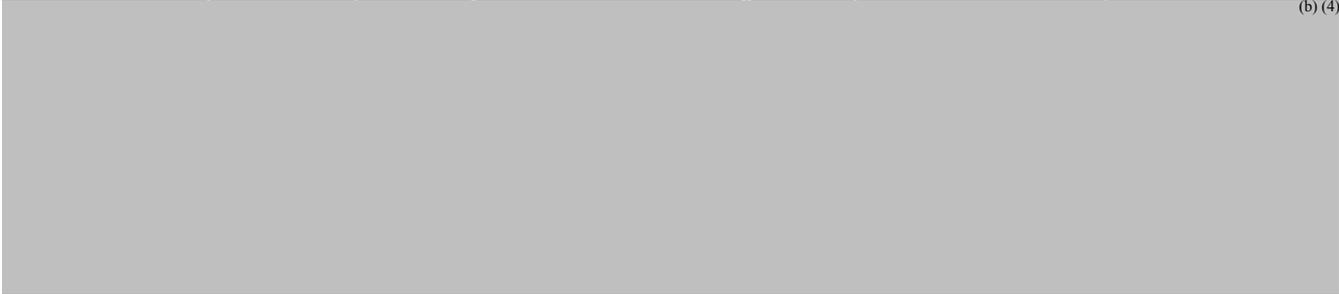
SDI’s VONA measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Information on the physician specialty, the patient’s age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

The Vector One® database integrates prescription activity from a variety of sources including national retail chains, mass merchandisers, mail order pharmacies, pharmacy benefits managers and their data systems, and provider groups. Vector One® receives over 2.0 billion prescription claims per year, representing over 160 million unique patients. Since 2002, Vector One® has captured information on over 8 billion prescriptions representing 200 million unique patients.

Prescriptions are captured from a sample of approximately 59,000 pharmacies throughout the US. The pharmacies in the data base account for nearly all retail pharmacies and represent nearly half of retail prescriptions dispensed nationwide. SDI receives all prescriptions from approximately one-third of the stores and a significant sample of prescriptions from the remaining stores.

**Table A.1: Total Dispensed Prescriptions for Hydrocodone Products**

**Table 1. Total Dispensed Prescriptions for Hydrocodone Products through U.S. Outpatient Retail Pharmacies, 2004-2007**



(b) (4)

**Table A.2: List of Analgesic and Respiratory Hydrocodone Products**

<i>Drug ID</i>	<i>Drugs of interest</i>	<i>Category</i>
d03075	hydrocodone	CNS
d03428	acetaminophen-hydrocodone	CNS
d03429	aspirin-hydrocodone	CNS
d04225	hydrocodone-ibuprofen	CNS
d03352	hydrocodone-pseudoephedrine	Respiratory
d03353	hydrocodone-phenylpropanolamine	Respiratory
d03366	hydrocodone/phenylephrine/pyrilamine	Respiratory
d03375	hydrocodone/pheniramine/PE/PPA/pyrilamine	Respiratory
d03915	hydrocodone-potassium guaiacolsulfonate	Respiratory
d04152	hydrocodone-phenylephrine	Respiratory
d04350	hydrocodone/potassium guaiacolsulfonate/PSE	Respiratory
d06669	hydrocodone/pseudoephedrine/triprolidine	Respiratory
d05426	brompheniramine/hydrocodone/phenylephrine	Respiratory
d04880	brompheniramine/hydrocodone/pseudoephedrine	Respiratory
d07067	chlorpheniramine/guaifenesin/hydrocodone/PSE	Respiratory
d03361	chlorpheniramine/hydrocodone/phenylephrine	Respiratory
d03416	chlorpheniramine/hydrocodone/PSE	Respiratory
d03356	chlorpheniramine-hydrocodone	Respiratory
d06058	dexbrompheniramine/hydrocodone/phenylephrine	Respiratory
d05365	dexchlorpheniramine/hydrocodone/phenylephrine	Respiratory
d04925	diphenhydramine/hydrocodone/phenylephrine	Respiratory
d03420	guaifenesin/hydrocodone/pheniramine/PPA/pyrilamin	Respiratory
d03414	guaifenesin/hydrocodone/pheniramine/PE/PPA	Respiratory
d03403	guaifenesin/hydrocodone/phenylephrine	Respiratory
d03404	guaifenesin/hydrocodone/pseudoephedrine	Respiratory
d03396	guaifenesin-hydrocodone	Respiratory

Source: Office of Applied Studies, SAMHSA, Drug Abuse Warning Network

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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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CATHERINE M DORMITZER  
08/21/2009

HINA S MEHTA  
08/26/2009

**NDA/BLA REGULATORY FILING REVIEW**  
**(Including Memo of Filing Meeting)**

<b>Application Information</b>		
NDA # 22-439 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: (b) (4) Established/Proper Name: hydrocodone, chlorpheniramine, and pseudoephedrine Dosage Form: oral solution Strengths: 5 ml contains: hydrocodone 5mg, chlorpheniramine 4mg, and pseudoephedrine 60mg		
Applicant: Cypress Pharmaceuticals, Inc. Agent for Applicant (if applicable): William Putnam, Ph.D., Beckloff Associates, Inc.		
Date of Application: November 6, 2008 Date of Receipt: November 7, 2008 Date clock started after UN:		
PDUFA Goal Date: September 7, 2009	Action Goal Date (if different): September 4, 2009	
Filing Date: January 6, 2009 Date of Filing Meeting: December 15, 2008		
Chemical Classification: (1,2,3 etc.) (original NDAs only) 4		
Proposed Indication(s): (b) (4) (b) (4)		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)	
<i>Refer to Appendix A for further information.</i>	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
Review Classification:  <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>  <i>If a tropical disease Priority review voucher was submitted, review classification defaults to Priority.</i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority  <input type="checkbox"/> Tropical disease Priority review voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/> Resubmission after refuse to file? <input type="checkbox"/>		
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device	
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify	

Other:	clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (if OTC product):	
List referenced IND Number(s): 102,177	
PDUFA and Action Goal dates correct in tracking system? <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established name to the supporting IND(s) if not already entered into tracking system.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are all classification codes/flags (e.g. orphan, OTC drug, pediatric data) entered into tracking system? <i>If not, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>Application Integrity Policy</b>	
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: <a href="http://www.fda.gov/ora/compliance_ref/aiplist.html">http://www.fda.gov/ora/compliance_ref/aiplist.html</a></i>  If yes, explain:  If yes, has OC/DMPQ been notified of the submission?  Comments:	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<b>User Fees</b>	
Form 3397 (User Fee Cover Sheet) submitted	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
User Fee Status  Comments:	<input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required
<i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. It is expected that all 505(b) applications, whether 505(b)(1) or 505(b)(2), will require user fees unless otherwise waived or exempted (e.g., business waiver, orphan exemption).</i>	
<b>Exclusivity</b>	

<p>Does another product have orphan exclusivity for the same indication? <i>Check the Electronic Orange Book at: <a href="http://www.fda.gov/cder/ob/default.htm">http://www.fda.gov/cder/ob/default.htm</a></i></p> <p><b>If yes, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?</b></p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES # years requested: 3 <input type="checkbox"/> NO
<p>If the proposed product is a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>):</p> <p>Did the applicant (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b) request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>	<input checked="" type="checkbox"/> Not applicable  <input type="checkbox"/> YES <input type="checkbox"/> NO
<b>505(b)(2) (NDAs/NDA Efficacy Supplements only)</b>	
<ol style="list-style-type: none"> <li>1. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</li> <li>2. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).</li> <li>3. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))?</li> </ol>	<input type="checkbox"/> Not applicable  <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO  <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO  <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO

<p><b>Note:</b> If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</p>			
<p>4. Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? <b>Check the Electronic Orange Book at:</b>  <a href="http://www.fda.gov/cder/ob/default.htm">http://www.fda.gov/cder/ob/default.htm</a></p>		<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO	
<p>If yes, please list below:</p>			
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration
<p>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</p>			
<b>Format and Content</b>			
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p> <p><b>Comments:</b></p>		<input type="checkbox"/> All paper (except for COL) <input type="checkbox"/> All electronic <input checked="" type="checkbox"/> Mixed (paper/electronic)  <input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)	
<p><b>If mixed (paper/electronic) submission</b>, which parts of the application are submitted in electronic format?</p> <p>All modules, as well as administrative forms, have been submitted electronically.</p>			
<p><b>If electronic submission:</b>  <u>paper</u> forms and certifications signed (non-CTD) or <u>electronic</u> forms and certifications signed (scanned or digital signature)(CTD)?</p> <p><i>Forms include: 356h, patent information (3542a), financial disclosure (3454/3455), user fee cover sheet (3542a), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p> <p><b>Comments:</b> Form 3542a was not submitted</p>		<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO	
<p><b>If electronic submission</b>, does it follow the eCTD guidance?  <a href="http://www.fda.gov/cder/guidance/7087rev.pdf">http://www.fda.gov/cder/guidance/7087rev.pdf</a></p> <p><b>If not</b>, explain (e.g., waiver granted):</p>		<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO	

<p><b>Form 356h:</b> Is a signed form 356h included?</p> <p><i>If foreign applicant, <b>both</b> the applicant and the U.S. agent must sign the form.</i></p> <p>Are all establishments and their registration numbers listed on the form?</p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>Index:</b> Does the submission contain an accurate comprehensive index?</p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:</p> <p><input checked="" type="checkbox"/> legible  <input checked="" type="checkbox"/> English (or translated into English)  <input checked="" type="checkbox"/> pagination  <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)</p> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>Controlled substance/Product with abuse potential:</b></p> <p>Abuse Liability Assessment, including a proposal for scheduling, submitted?</p> <p>Consult sent to the Controlled Substance Staff?</p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable  <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO  <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>BLAs/BLA efficacy supplements only:</b></p> <p>Companion application received if a shared or divided manufacturing arrangement?</p> <p><b>If yes, BLA #</b></p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	
<p>Patent information submitted on form FDA 3542a?</p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<b>Debarment Certification</b>	
<p>Correctly worded Debarment Certification with authorized signature?</p> <p><i>If foreign applicant, <b>both</b> the applicant and the U.S. Agent must</i></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><b>sign the certification.</b></p> <p><i>Note: Debarment Certification should use wording in FD&amp;C Act section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p> <p><b>Comments:</b></p>	
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	
<p>Field Copy Certification: that it is a true copy of the CMC technical section (<i>applies to paper submissions only</i>)</p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<p><input checked="" type="checkbox"/> Not Applicable (<i>electronic submission or no CMC technical section</i>)</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<b>Financial Disclosure</b>	
<p>Financial Disclosure forms included with authorized signature?</p> <p><i>Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an Agent.</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<b>Pediatrics</b>	
<p><b><u>PREA</u></b></p>	
<p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	
<p>Are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES</p> <p><input checked="" type="checkbox"/> NO</p>
<p><b>If no</b>, is a request for full waiver of pediatric studies OR a request for partial waiver/deferral and a pediatric plan included?</p>	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> <li>• <i>If no, request in 74-day letter.</i></li> <li>• <b>If yes</b>, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3)</li> </ul>	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<p><b>Comments:</b> Application specified 21 CFR 314.55(c)(2)</p>	

<b>BPCA (NDAs/NDA efficacy supplements only):</b>	
Is this submission a complete response to a pediatric Written Request?  <i>If yes, contact PMHS (pediatric exclusivity determination by the Pediatric Exclusivity Board is needed).</i>  <b>Comments:</b>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<b>Prescription Labeling</b>	
Check all types of labeling submitted.  <b>Comments:</b>	<input type="checkbox"/> Not applicable <input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use <input type="checkbox"/> MedGuide <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)
Is electronic Content of Labeling submitted in SPL format?  <i>If no, request in 74-day letter.</i>  <b>Comments:</b>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Package insert (PI) submitted in PLR format?  <b>If no</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If before</b> , what is the status of the request?  <i>If no, request in 74-day letter.</i>  <b>Comments:</b>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?  <b>Comments:</b>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
MedGuide or PPI (plus PI) consulted to OSE/DRISK? ( <i>send WORD version if available</i> )  <b>Comments:</b>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
REMS consulted to OSE/DRISK?  <b>Comments:</b>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
Carton and immediate container labels, PI, PPI, and proprietary name (if any) sent to OSE/DMEDP?  <b>Comments:</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<b>OTC Labeling</b>	
<p>Check all types of labeling submitted.</p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> <b>Not Applicable</b> <input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)
<p>Is electronic content of labeling submitted?</p> <p><i>If no, request in 74-day letter.</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Are annotated specifications submitted for all stock keeping units (SKUs)?</p> <p><i>If no, request in 74-day letter.</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>If representative labeling is submitted, are all represented SKUs defined?</p> <p><i>If no, request in 74-day letter.</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Proprietary name, all labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEDP?</p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<b>Meeting Minutes/SPA Agreements</b>	
<p>End-of Phase 2 meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES Date(s): <input checked="" type="checkbox"/> NO
<p>Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES Date(s): <input checked="" type="checkbox"/> NO
<p>Any Special Protocol Assessment (SPA) agreements?</p> <p><i>If yes, distribute letter and/or relevant minutes before filing meeting.</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES Date(s): <input checked="" type="checkbox"/> NO

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** January 15, 2008

**NDA/BLA #:** 22-439

**PROPRIETARY/ESTABLISHED NAMES:** (b) (4)

**APPLICANT:** Cypress Pharmaceuticals

**BACKGROUND:** 505(b)(2) application for a marketed unapproved drug

**REVIEW TEAM:**

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Philantha M. Bowen	Y
	CPMS/TL:	Sandy Barnes	N
Cross-Discipline Team Leader (CDTL)	Wei Qiu,		Y
Clinical	Reviewer:	Theresa Michele	Y
	TL:	Sally Seymour	Y
Social Scientist Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		
Labeling Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		
OSE	Reviewer:		
	TL:		
Clinical Microbiology ( <i>for antimicrobial products</i> )	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Sandra Suarez	N
	TL:	Wei Qiu	Y
Biostatistics	Reviewer:	Same as TL	
	TL:	Qian Li	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Virgil Whitehurst	Y
	TL:	Timothy Robison	Y
Statistics, carcinogenicity	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Xiaobin Shen	Y
	TL:	Prasad Peri Ali Al-Hakim	Y N
Facility ( <i>for BLAs/BLA supplements</i> )	Reviewer:		
	TL:		
Microbiology, sterility ( <i>for NDAs/NDA efficacy supplements</i> )	Reviewer:		
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Other reviewers			

**OTHER ATTENDEES:**

505(b)(2) filing issues?  <b>If yes, list issues:</b>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
Per reviewers, are all parts in English or English translation?  <b>If no, explain:</b>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><b>Electronic Submission comments</b></p> <p><b>List comments:</b> Administrative forms and modules are all electronic</p>	<input type="checkbox"/> Not Applicable
<p><b>CLINICAL</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b> Product not BE, thus no DSI will be requested; See Clinical Pharmacology filing review dated 1/9/09</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <li><i>this drug/biologic is not the first in its class</i></li> <li><i>the clinical study design was acceptable</i></li> <li><i>the application did not raise significant safety or efficacy issues</i></li> <li><i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined  Reason:
<ul style="list-style-type: none"> <li>If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b> Refer to Clinical Comment</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p><b>BIOSTATISTICS</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>PRODUCT QUALITY (CMC)</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p><b>If no</b>, was a complete EA submitted?</p> <p><b>If EA submitted</b>, consulted to EA officer (OPS)?</p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Establishment(s) ready for inspection?</li> <li>Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ?</li> </ul> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<ul style="list-style-type: none"> <li>• Sterile product?</li> </ul> <p><b>If yes, was Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)</b></p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>FACILITY (BLAs only)</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter

**REGULATORY PROJECT MANAGEMENT**

**Signatory Authority:** Badrul A. Chowdhury, M.D., Ph.D.

**GRMP Timeline Milestones:**

Filing Meeting	12/15/08
Filing Date	1/6/09
74 Day Letter	1/20/09
MCR Meeting	3/31/09
Primary Reviews Due	7/7/09
Secondary Reviews Due	7/14/09
Complete CDTL Review	7/27/09
Full Labeling Meeting	6/5/09
WU Meeting	6/29/09
Labeling T-con w/sponsor	8/5/09
PDUFA Date	9/7/09 (Actual 9/4/09)

**Comments:**

**REGULATORY CONCLUSIONS/DEFICIENCIES**

<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><input checked="" type="checkbox"/> Standard Review</p> <p><input type="checkbox"/> Priority Review</p>

**ACTIONS ITEMS**

<input checked="" type="checkbox"/>	Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into tracking system.
<input type="checkbox"/>	If RTF action, notify everybody who already received a consult request, OSE PM., and Product Quality PM. Cancel EER/TBP-EER.
<input type="checkbox"/>	If filed and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	If BLA or priority review NDA, send 60-day letter.
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Other

## Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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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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PHILANTHA M BOWEN  
07/30/2009

SANDRA L BARNES  
08/05/2009

# REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

## Division of Pulmonary and Allergy Products

**Application Number:** NDA 22-439

**Name of Drug:** (b) (4) (hydrocodone, chlorpheniramine, and pseudoephedrine) oral solution

**Applicant:** Cypress Pharmaceuticals

### Material Reviewed:

**Submission Date(s):** November 6, 2008

**Receipt Date(s):** November 7, 2008

**Submission Date of Structure Product Labeling (SPL):** November 6, 2008

**Type of Labeling Reviewed:** Package Insert

### Background and Summary

On November 6, 2008, Cypress Pharmaceuticals submitted a supplemental New Drug Application for (b) (4) for the (b) (4) (b) (4)

The proposed labeling text for (b) (4) was provided in SPL, including carton and container labels. Draft labeling text was submitted in Word format (.doc) for review on November 6, 2008.

### Review

The WORD and SPL versions of the proposed labeling in the new PLR format was reviewed using the Label Review Tool provided by SEALD.

Address the identified deficiency/issue and re-submit the labeling. This updated version of labeling will be used for further labeling discussions.

The following comments pertain to the Highlights and the Full Prescribing Information-Details section of the product label:

Do not use the “TM” or “R” symbols after the drug names in the Highlights section of the label. In addition, remove the “TM” symbols following the drug name in the detailed Full Prescribing Information (FPI). These symbols may be used once upon first use in the FPI. This format is recommended because symbols may not appear in the SPL version of labeling and the WORD version should match the SPL version as much as possible.

### **Recommendations**

Comments/recommendations for the proposed labeling have been identified and will be conveyed to the applicant in the 74-day letter.

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Philantha M. Bowen  
Regulatory Project Manager  
CDER, OND, ODE II

Supervisory Comment/Concurrence:

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Sandy Barnes  
Chief, Project Management Staff  
CDER, OND, ODE II

Drafted: Bowen/January 12, 2009

Initialed: Barnes/July 16, 2009

Finalized: Bowen/July 27, 2009

Filename: N22-439 PM PLR Review

**CSO LABELING REVIEW OF PLR FORMAT**

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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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PHILANTHA M BOWEN  
07/28/2009

SANDRA L BARNES  
08/05/2009

# MEMORANDUM

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

**DATE:** April 8, 2009

**TO:** NDA 22439 and NDA 22442 (b) (4)

(b) (4)

**THROUGH:** Ali Al-Hakim, Ph.D., Chief, Office of New Drug Quality Assessment, Division of Pre-Marketing Assessment I, Branch II

Prasad Peri, Ph.D., Pharmaceutical Assessment Lead, Office of New Drug Quality Assessment, Division of Pre-Marketing Assessment I, Branch II

Xiaobin Shen, Ph.D., Quality Reviewer, Office of New Drug Quality Assessment, Division of Pre-Marketing Assessment I, Branch II

Sheldon Markofsky Ph.D., Quality Reviewer, Office of New Drug Quality Assessment, Division of Pre-Marketing Assessment I, Branch II

**FROM:** Philantha Bowen, M.P.H., RN, Senior Regulatory Management Officer, Division of Pulmonary and Allergy Products, Office of Drug Evaluation II

**SUBJECT:** **CMC Inquiry: Leachables in hydrocodone containing NDA products**

The following CMC inquiry was received, via e-mail correspondence, on February 10, 2009, from Dr. William Putnam of Beckloff Associates, consultant for Cypress Pharmaceuticals:

*We are in the process of preparing our responses to the comments presented in the filing letters for the hydrocodone containing NDA products (NDA 022439 (b) (4) and NDA 022442). One of the questions involves provision of information related to the leachables in our drug products. I know that you, Dr. Prasad Peri, and Cypress Pharmaceutical, Inc. (Janet DeLeon and Rob Lewis) have had a couple of communications related to this topic and the information required to fulfill this requirement during the IND phase of this product. Based on that information we have prepared the following response.*

*Would it be possible for you to check with the chemistry reviewer to determine if this response would be sufficient to fulfill the response?*

- 7. An assessment of leachables in the drug product was not provided in the NDA. Submit the results of your evaluation of extractables and leachables from the container closure system and how you concluded that they do not exist and are not necessary for routine monitoring. We strongly recommend that you use appropriate analytical methods that are capable of monitoring and separating these compounds from other degradants and impurities in the drug product. Leachables specifications should be proposed when the data in your drug product have reached an asymptote.*

## **Response**

*Cypress requested clarification to a similar earlier request in an e-mail to Lt. Philantha Bowen, Senior Regulatory Management Officer, FDA on February 18, 2008. Lt. Bowen responded on February 29, 2008 with the following comment: "...All the stability time points should be pulled and tested as per the stability protocol for impurities (using a validated stability indicating method). Any unknown impurity found above the ICH Q3B(R) identification and qualification threshold needs to be identified and acted on per the guidance. If these impurities are detected and not related to the drug substance or excipients, and are identified of extraneous source (possibly container closure system), they are termed leachables...". Therefore, Cypress' validated test method for identification and quantitation of impurities will be used to detect any possible leachables as requested. This validated test method is used at product release and at each stability time point to evaluate the drug product for impurities arising from the drug substance, excipients, and extraneous sources such as the container closure system. Of note, through 6 months of ICH accelerated ( $40 \pm 2$  °C/ $75 \pm 5\%$  relative humidity) and room temperature ( $25 \pm 2$  °C/ $60 \pm 5\%$  relative humidity) no impurities arising from extraneous sources have been found to be above the ICH identification threshold.*

CMC reviewed the response and communicated via e-mail on February 13, 2009, that the sponsor's response was acceptable. Eunice Chung, Regulatory Project Manager, left a voice message for Dr. Putman on February 18, 2009, informing him of the acceptability of Cypress' response from the CMC standpoint.

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/s/

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Philantha M Bowen  
4/8/2009 11:35:17 AM  
CSO

**MEMORANDUM**

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

**DATE:** February 29, 2008

**TO:** Janet DeLeon, Associate Director Product Development, Cypress Pharmaceuticals

**THROUGH:** Charles E. Lee, M.D., Clinical Team Leader, Division of Pulmonary and Allergy Products

Xu Wang, M.D., Clinical Reviewer, Division of Pulmonary and Allergy Products

Wei Qiu, Ph.D., Acting Clinical Pharmacology Team Leader, Division of Clinical Pharmacology 2

Suarez, Sandra, Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology 2

**FROM:** Philantha Bowen, MPH, RN  
Sr. Regulatory Project Management Officer, Division of Pulmonary and Allergy Products

**SUBJECT:** Clarification of January 14, 2008, Pre-IND Meeting Minutes

**APPLICATION/DRUG:** IND (b) (4)

(b) (4)

Hydrocodone/Pseudoephedrine Oral Solution  
Hydrocodone/Chlorpheniramine/Pseudoephedrine Oral Solution

In an e-mail correspondence received February 14, 2008, Janet DeLeon of Cypress Pharmaceuticals requested clarification of the January 14, 2008, meeting minutes regarding the post meeting comments (b) (4). Ms. DeLeon provided the Division with the following information as stated:

*After reviewing the minutes, we have two items that we would like to discuss with the Agency.*



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Philantha M. Bowen, MPH, RN  
Sr. Regulatory Management Officer

Linked Applications

Sponsor Name

Drug Name

IND (b) (4)

CYPRESS PHARM

(b) (4)  
ORAL SOLTN

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/s/

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PHILANTHA M BOWEN

02/29/2008

Regulatory Project Manager